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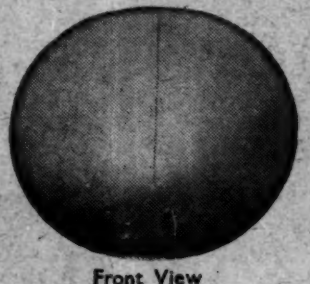

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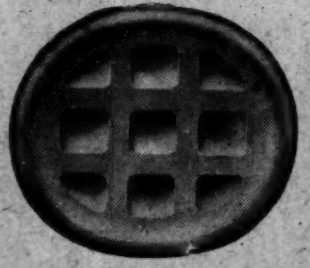

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 27 1952

BACTERIOPHAGE-TYPING AND EPIDEMIOLOGICAL PROBLEMS*

BY

J. S. K. BOYD, O.B.E., M.D., F.R.C.P., F.R.S.

Director, Wellcome Laboratories of Tropical Medicine; Brigadier, late R.A.M.C.

The name of Edward Jenner is so closely associated with smallpox and cowpox and calf lymph, with dramatic episodes such as the successful vaccination of James Phipps, and with the long and acrimonious arguments which since that day have ranged round the subject of vaccination in general, that one is apt to feel a memorial lecture which is unrelated to these matters fails in its purpose. However, this is far from being the case. It is by no means improbable that this versatile scientist and naturalist, whose activities covered a wide range of subjects, was more interested in his ornithological observations than in his excursions into the realms of virus disease, and had more inner satisfaction in being the first to observe the young cuckoo "murderously evict the rightful tenants of the nest" than in his discovery of how to prevent smallpox. We can be sure that a curious and questing mind such as his would have found more than a little to interest him in the subject I have chosen for my lecture.

One of the principal tasks of an epidemiologist entrusted with the investigation of an outbreak of infectious disease is to locate its source and to plot its spread, so that effective steps can be taken to arrest its progress. In the days of clinical diagnosis this was a haphazard process except when the signs and symptoms of the disease were so striking that no mistake could be made. Inevitably, the symptomless carrier was missed. The advent of methods which enabled the causative organism to be identified in cases of bacterial disease added greatly to the precision of such investigations, though even at this stage the position was far from satisfactory. In typhoid fever, for instance, the evidence linking a remote carrier with an outbreak was often tenuous, and frequently it was impossible to say with certainty whether any particular carrier was or was not responsible. The position has been completely changed by the discovery and application of bacteriophage-typing, which enables a number of distinct "lines" or "races" or, as they are usually called, "types" of otherwise indistinguishable typhoid bacilli to be identified with certainty. The number of types of *Salmonella typhi* now described is 29, and the test by which they can be recognized is one of great delicacy and accuracy. The ability to identify these types goes far to narrow down an investigation and makes it possible to reach conclusions which previously were quite unjustifiable.

This point is well illustrated by an interesting example which was, as it happens, the first practical application of phage-typing in this country. A supply of the very limited range of type phages then available had been sent to me by Dr. Craigie, and the technique of using them had just been mastered, when a naval colleague who, like myself, was working with typhoid bacilli came to me in some distress because his technician had developed a severe attack of typhoid fever which he feared might be a laboratory infection. The man's movements in the previous few weeks introduced various complications. He came from Edinburgh to join the staff of the Royal Naval Medical School on December 7, 1938. When in Edinburgh he had been working in a laboratory which at that time was investigating typhoid bacilli isolated from an outbreak at Hawick. He returned to Edinburgh for his Christmas vacation from December 22 until January 3, 1939. The first symptoms appeared on January 14. Where had he picked up his infection? By a happy chance, an answer to this query was found when the various strains of *Salm. typhi* were typed. The Hawick organism had peculiar characters and was at the time regarded by Craigie as a variant of Type A. The only three cultures kept in the naval laboratory proved to be Types A, E, and F. The strain recovered from the patient was Type C. He had therefore acquired his infection privately, presumably when on holiday.

This incident occurred early in 1939. A great expansion in the scope and in the application of this technique has taken place since then. Many new types of typhoid bacilli have been discovered, and typing schemes have been evolved for several other bacteria.

LABORATORY ASPECTS OF PHAGE-TYPING

Phage-typing and Antigenic Structure

All "smooth" bacteria have an O, or somatic, antigen which is of considerable stability, being resistant, within limits, to the action of heat, alcohol, and acid. Certain members of the *Salmonella* group have a second antigen, best exemplified in the Vi antigen of *Salm. typhi*. This is altered by heat and by alcohol, and destroyed by a concentration of acid which does not affect the O antigen (Felix and Pitt, 1936). An identical Vi antigen is present in *Salm. paratyphi* C and in certain members of the coli group. Felix and Pitt describe a similar or at least a related type of antigen in *Salm. paratyphi* A, *Salm. paratyphi* B, and *Salm. typhi-murium*.

The relationship of certain phages and O antigens has long been recognized. When the Vi antigen of *Salm. typhi* was identified by Felix and Pitt (1934) various workers began to study the reaction of phages against bacteria endowed with this antigen. The most fruitful

*Jenner Memorial Lecture delivered at St. George's Hospital Medical School on May 20, 1952.

researches were those of Craigie and Brandon (1936), who isolated four different phages active against Vi-containing *Salm. typhi* but inactive against strains containing only O antigen (the so-called W strains). They thus established the existence of Vi phages as distinct from O phages. Felix and Callow (1943) found a Vi phage active against *Salm. paratyphi* B and *Salm. typhi-murium*.

Two systems of phage-typing have been built round these two groups of phages. Vi-typing, mainly clear-cut and precise, is applicable to bacteria which possess Vi antigen. O-typing, less specific and less precise, is used in the case of organisms which have O but not Vi antigen.

Preparation of Typing Phages

Lysate containing phage for typing can be prepared in several ways. The simplest is to inoculate an actively growing broth culture of the organism with the phage in question and incubate until clearing takes place—usually within two hours. Any surviving bacteria are then either killed by heating or removed by filtration. The resulting clear lysate, which contains a high concentration of phage particles, is titrated by placing standard drops of a series of decimal dilutions on a plate of suitable nutrient agar previously sown with the homologous organism, and incubating overnight. The appearance of the resultant patches varies from confluent lysis, caused by fusion of many plaques, to a few scattered discrete plaques taking origin from single phage particles. For typing purposes the phage is used at the dilution which just gives confluent lysis (the so-called critical test concentration). This is likely to be somewhere between two of the decimal dilutions in the original titration. The making of pure phages for typing is a very tricky business, not to be undertaken lightly. For reliable results it is essential that they should be prepared by an experienced worker in a central laboratory specializing in this subject, and that each batch should be subjected to exhaustive tests to ensure its purity.

Vi-phage-typing

Conditioned or Adapted Phages.—Craigie and Yen (1938) were the first to observe the phenomenon which led to the development of Vi-phage-typing. They noticed that one of the four types which they isolated—Type II—was active against some strains of *Salm. typhi* but not against others. However, when this phage was tested in strong concentration against one of these recalcitrant strains sown on a solid medium, a few plaques developed. If the phage from one of these plaques was further propagated on the resistant strain it reproduced itself in such a way that a lysate with a high titre for this erstwhile resistant strain was evolved after a few passages. This new phage had little or no action on the original bacterial strains against which the parent phage was active. In this way a conditioned or adapted phage was produced, and by the selective action of this and of the parent phage it became possible to identify these two races of *Salm. typhi*. By a wide and general application of this principle an increasing number of phage types of *Salm. typhi* have been identified, and, as already mentioned, some 29 are now described, each of which can be recognized with a high degree of certainty by the use of a conditioned or adapted variant of Craigie's Vi phage Type II. Within the total of 29 are certain small groups of related types, one of five, one of three, and three of two, but these subtypes are easily distinguished from each other.

Phage-typing an Unknown Strain of Salm. typhi.—To type an unknown strain a plate of nutrient agar (the composition of the medium is of some importance) is sown with a suspension of the organism and allowed to dry. This is then spotted on marked sites with drops of a series of phage preparations, each diluted to its critical test concentration. It is time-saving to have separate phage lysates for the common bacterial types and one or more mixtures of lysates of the remaining rarer types. It is well, too, to include a patch with Craigie's Type I Vi phage, which is active against all Vi strains and hence can be used to detect W strains. The plate is incubated overnight, and next morning examined for patches of lysis. If confluent lysis is produced by one of the monovalent phages there is no need to proceed further, as this reveals the phage type of the organism; if produced by one of the multivalent mixtures it will be necessary to repeat the test with the monovalent phages of which this is made up, to identify the exact type causing the lysis. Type A is lysed by all the adapted phages. "Untypable" strains are lysed by Phage I only. W strains show no lysis at all.

Untypable Bacterial Strains.—In the early days of phage-typing significant numbers of strains containing Vi antigen were found to be untypable. Many of these have now been identified as new types, but some cannot be accounted for in this way. Inhibition of phage action in such cases is apparently due to interference by latent or symbiotic phage present in the bacillus. Certain anomalous subtypes are believed to owe their origin to the same cause. Although this is a complicated problem it affects only a minority of strains and does not detract from the general usefulness of the method.

Persistence of Phage-type Characters.—Experience has shown that, with minor exceptions, these phage types of *Salm. typhi* breed true, so that a bacterial strain maintains its type indefinitely throughout succeeding generations. It is this continuity which gives to these characters their epidemiological significance.

Typing of Salm. paratyphi A, *Salm. paratyphi* B, *and Salm. typhi-murium.*—In India, Dhayagude and Banker (1952) have isolated a phage which has a specific action on *Salm. paratyphi* A. No results have yet been published to show whether this phage is adaptable or if a typing system has been evolved. Felix and Callow (1943) have developed a method of Vi-phage-typing, similar to that used for *Salm. typhi*, which can be applied to *Salm. paratyphi* B and *Salm. typhi-murium*. Ten phage types of *Salm. paratyphi* B are now recognized (Felix and Callow, 1951). However, the interaction of these typing phages with the different strains of *Salm. paratyphi* B does not give the clear-cut and specific results which are found in typing *Salm. typhi* with adaptations of Craigie's Type II phage. Instead of being picked out by one specific phage, most of the bacterial types give a pattern of reactions with the different typing phages. Further, variations occur in the reaction pattern of several bacterial types in such a way that the picture is suggestive of the results given with O phages, which are described later. The authors of this method point out that 2 of the 10 typing phages are not adapted from the same original phage as are the others, and that the 10 phages fall into three different antigenic groups. These facts suggest that contamination of the original phage has taken place. Felix and Callow attribute these "irregularities" to the presence of "natural" (symbiotic) phages in the different strains of *Salm. paratyphi* B, which not only affect the resistance of the bacteria to different phages but render it difficult if not impossible to make pure phage preparations for typing. Despite these shortcomings the scheme is reported to work well in practice, and between 1942 and 1950 90% of the strains of *Salm. paratyphi* B isolated in Britain were successfully typed in the Enteric Reference Laboratory. No details have been published regarding the typing of *Salm. typhi-murium*.

O-phage-typing

Many unsuccessful attempts have been made to adapt O phages to different strains of an organism in the same way as Vi phage Type II has been adapted to *Salm. typhi*. O-phage-typing is carried out by using a series of phages derived from different bacterial strains. Some of these pick

out specific types of the organism. Thus, Wilson and Atkinson (1945), who evolved the scheme which is still used for typing staphylococci, found that 11 of the 21 phages they prepared were monovalent in that they lysed only one type of staphylococcus. More commonly these O phages act on several bacterial types but not on others. When cultures are tested with a series of phage preparations different patterns of reaction are given by which the bacterial types can be recognized. Such patterns of reaction are to be seen in the first three groups of "subtypes" described by Wilson and Atkinson, but are perhaps best illustrated by Lilleengen's scheme (1948) for *Salm. typhi-murium*. Hammarström (1949) has developed a similar but very complicated method for *Shigella sonnei*, and schemes have also been put forward for *Pseudomonas pyocyanea* (Warner, 1950) and certain *Salmonella* strains.

The typing of staphylococci by O phages, although it has its shortcomings, has proved to be of great practical value. Certain types—and these the common ones—are relatively constant in the pattern they give. Others are more variable, and it may be difficult to ascribe them to a definite type. Nevertheless, in any one outbreak of infection the pattern of lysis in the pathogenic strain is constant, so that it is possible in this way to link up cases and carriers.

Underlying Cause of the Phage-type Phenomenon

It has long been recognized that the phenomenon of the phage type is in some way connected with the presence in the bacteria which are being examined of phages of the kind variously known as "natural" or "latent" or, as I prefer to call them, "symbiotic." This was pointed out by Craigie (1942), who showed that "imperfect" or "untypable" Vi strains owe their peculiar characters to the presence of such a phage. Recently Felix and Anderson (1951) have found that the presence of symbiotic phage in *Salm. typhi* Type F2 is responsible for the difference between this type and F1. Further, they have isolated symbiotic phages from 11 of the 29 established types of *Salm. typhi*, and have shown that by grafting certain of these on to *Salm. typhi* Type A (which is apparently free from symbiotic phage) they were able to convert Type A into types either identical with or closely related to those from which the symbiotic phage was isolated. Nicolle and his colleagues (1951) have effected similar transformations of type in *Salm. paratyphi* B by means of phage from lysogenic strains. There can be little doubt that the phage type of an organism is bound up with some specific immunity or resistance which, in some cases at least, it derives from the symbiotic phage it carries. Typing-phages presumably function because they are endowed with the capacity of overcoming this resistance.

A Direct Method of Phage-typing

If symbiotic phage is responsible for the phage type of the organism which carries it, then typing methods which function by detecting the changes produced in the organism by the symbiotic phage must be regarded as indirect. Further, such methods may be incapable of giving a clear-cut answer when the organism contains more than one type of symbiotic phage—a state of affairs which is by no means uncommon. On the other hand, a direct approach to the problem can be made by isolating and identifying the phage or phages with which the organism is infected. This method was suggested some years ago by an unexpected finding during an investigation of the symbiotic phages of *Salm. typhi-murium*. Two cultures, each labelled *Salm. typhi-murium* Copenhagen and believed to be alike, although they were received in the laboratory at different times, were found to contain different varieties of symbiotic phage. As infection with symbiotic phage is, with rare exceptions, permanent and not subject to change, this finding was rather unexpected. Inquiry revealed that the two strains were in reality of different origin. This observation focused attention on the possibility of using the symbiotic phage as an additional characteristic or "mark" by which the bacteria could be "typed": in other words, of identifying strains of bacteria in terms of the symbiotic bacteriophage which they carry. Such a method is feasible only when an exact classification of the symbiotic phages found in a strain of bacteria (*Salm. typhi, Salm. paratyphi* B, *Salm. typhi-murium*, etc.) has been worked out and when the characters of each symbiotic phage have been defined in such a way that it can be identified with certainty and without undue delay and difficulty.

This has now been done in the case of *Salm. typhi-murium* (Boyd, 1950). For identifying symbiotic phage it is necessary to have one or more indicator strains—that is, cultures of the organism which are either free from symbiotic phage or contain one so weak that it does not produce resistance to, or interfere with the action of, the phages which are found in other strains of the organism. Two such indicator strains have been used in the work on *Salm. typhi-murium*. On these the different symbiotic phages are propagated and can be made to reveal their characteristic plaque characters. The identity of the symbiotic phages, which fall into two groups, can in most cases be established by the appearance of the plaques and can be confirmed, where necessary, by serological methods, by the thermal death-point, by reaction on different indicator strains, and by a few special tests which need not here be described. Twelve different symbiotic phages for *Salm. typhi-murium* are now recognized, and, as certain of them may occur in combination, a wide range of "marks" is provided.

With the co-operation of Dr. Parker and Dr. Mair, of the Monsall Hospital, Manchester, this method of typing has now been given a two-year trial, some 446 strains having been examined. The findings have corresponded closely with epidemiological expectations, and the method has proved to be one of great accuracy. Nevertheless it has its shortcomings. It is more laborious than the Vi-phage-typing method, involves the use of more culture media, and takes longer to put through. At best, results are not available for 48 hours, and may take three to four days. The method has been criticized on the grounds that symbiotic phages are so numerous and diverse that it is not practicable to identify them by this technique. In investigations which have now gone on for over four years, during which time bacterial strains have been received from all parts of the country, this has not proved to be a difficulty.

This method will never rival or replace the simple and exact technique used for the Vi-phage-typing of *Salm. typhi*. It is possible, though on the whole unlikely, that it may one day replace the method now in use for *Salm. paratyphi* B, which is becoming rather involved. It may well prove in the long run to be the best way of typing bacteria which do not possess Vi antigen and which are at present typed, if at all, by O phages.

EPIDEMIOLOGY

Soon after its introduction phage-typing became established as a procedure capable of affording much assistance to the epidemiologist. In 1940 the Emergency Public Health Laboratory Service adopted it as a routine method of investigation, and since then there has been a steady build-up of the organization. Subsequently, the International Association of Microbiologists has interested itself, and arrangements now exist for international co-operation. This aims at integrating the work in different countries and ensuring that comparable results are obtained. In time this plan will enable a world-wide survey to be made, from which much valuable information is likely to accrue.

Typhoid Fever

Various reports have been published of outbreaks of typhoid fever where phage-typing has helped to solve a problem which otherwise would have remained a mystery. Perhaps the best example is to be found in the account given by Bradley (1943) of a series of sporadic cases which occurred in 1941 and 1942. This is not a new story, but it will bear retelling.

The first case was notified from Hertfordshire, and attracted particular attention because the organism isolated proved to be

Type D4, a variety not previously found in this country. In a little under two years a further 22 cases occurred—18 in Buckinghamshire, two in London, one in Kent, and one in Wiltshire. In the series there were a few small groups of associated cases, but the majority of infections were sporadic and apparently unrelated. All, however, were caused by Type D4, and there could be no reasonable doubt that they originated from a common source. A careful investigation showed that the only common factor was the milk supply. This was traced through the Hertfordshire Milk Distributing Depot to a group of 13 farms in Wiltshire which sent milk to this depot. All these farms were inspected, and four were investigated in detail with negative results. The clue which led to the solution of the problem was provided by the sixteenth case of the series, which occurred in Wiltshire. When this patient was questioned it transpired that at the time of his infection he had been working in one of the suspect Wiltshire farms. Attention was at once directed to this farm, and very soon it was discovered that the farmer himself was a chronic carrier of D4.

But for the precise information afforded by phage-typing, which might be compared to the finger-prints of the criminal, suspicion would never have been focused on this particular farm, and the carrier might still have been the cause of recurring cases of infection, perhaps even of an explosive epidemic. Not the least interesting part of this story, as Bradley points out, is the revelation that milk-borne infection does not necessarily conform to the pattern of the classical explosive outbreak.

Similar, if less dramatic, accounts are to be found in the literature of different countries throughout the world, and they leave no doubt that phage-typing in typhoid fever has established its claim as a method which can be of unique value in revealing the chronic carrier who constitutes the reservoir of infection.

Wartime Experience in the Middle East

Most published accounts are concerned with the detection of typhoid fever in a stationary population. It was my good fortune to have the opportunity of using it in following the ebb and flow of typhoid infection in what was undoubtedly one of the most fluid populations which have ever existed—that of the Middle East during the three years when it was a theatre of active operations in the last war. I was armed with the limited number of type phages then available (some with a different designation from that now used), all of which had been given to me by Dr. Craigie. The bacterial strains for typing came from a wide variety of sources. The majority were from the laboratories of the hospitals of the British and Commonwealth Forces—but these were scattered throughout Egypt, Libya, Cyrenaica, Tripolitania, Malta, Cyprus, Syria, Palestine, Iraq, Iran, Sudan, and Eritrea. Other cultures came from the civilian public health laboratories in Cairo and Palestine, some from the American University of Beirut. The patients from whom the strains were isolated were members of the Allied Fighting Forces, prisoners of war, refugees, and the normal civilian inhabitants of the Middle East countries. The cultures examined were in some instances a limited selection derived from a large number of related cases. In all, 1,386 strains were typed.

These observations began at the end of 1940, and the first batch of cultures came from Italian prisoners of war, of whom we captured some 120,000 in December, 1940, and January, 1941. These men had to be hurriedly accommodated in camps in the Suez Canal Zone. Their numbers were both unexpected and embarrassing, as we were unprepared for so many involuntary guests. At first sanitary arrangements in general were unavoidably primitive, and in the circumstances we feared there might be major epidemics of infectious disease, but by good fortune these fears did not materialize. There was, however, a small outbreak of typhoid fever which developed from infection present among the prisoners when they were captured. This lasted for about two months. Without exception all cultures from this outbreak were Type G. Although this type caused no further significant outbreaks, it continued to haunt us during the next three years, and appeared sporadically in military personnel and prisoners of war. Curiously enough, it did not occur among cultures from civilian sources in Egypt, of which 50, supplied at random from the public health laboratory, belonged to Types A, B4, C, H, L, and M.

Further Outbreaks

After a free interval of about three months cases of typhoid infection again began to appear in another group of prisoner-of-war camps, and by June a major outbreak was in progress which reached its peak in July, declined in August, and came to an end in September. Two phage types, B4* and C, were responsible. Simultaneously with these typhoid cases, an outbreak of infection with *Salm. paratyphi* A started in May and continued until October, reaching a higher level than did the typhoid epidemic.

Although not strictly relevant, it might be of interest to record the inoculation history of these prisoners. Stocks of British Army T.A.B. vaccine were too low to allow it to be issued for their use at the time of their capture, nor could it be procured immediately, for at that period of the war supplies took from six to nine months from the date of requisition to get to Egypt from the United Kingdom. However, ample stocks of vaccine of Italian origin had fallen into our hands, and steps were taken to ensure that all prisoners were inoculated with this. During the summer of 1941 adequate supplies of our own vaccine were received, and thereupon the prisoners were promptly reinoculated. Whether *post hoc* or *propter hoc* it is impossible to say, but no further outbreak of enteric group fever of any significance occurred among these men, and there was a period of calm in the camps until the end of October, 1942, when a further series of prisoners arrived from Alamein.

In this interval, however, a storm blew up from another quarter. In the early months of 1942 some 80,000 to 100,000 Poles of both sexes and all ages were transferred from Russia to the care of the Western Allies. This move was carried out before adequate preparations could be made to receive the immigrants. They were shipped to Pahlevi, a Persian port on the Caspian Sea, and handed over to us there, whence they were taken to the cities of Kazvin and Teheran. Many of them were extremely ill, and some presented the unmistakable symptoms of old-world typhus fever, a fact which caused us very grave concern. It transpired, however, that these were late cases in an epidemic which was all but burnt out, and the application of the usual measures of disinfestation, although far from easy in the circumstances, soon brought it to an end. To our great relief no outbreak of typhus occurred among the civilian population. From the first there was considerable doubt whether all the cases were typhus fever, and when adequate means of laboratory diagnosis became available there was no difficulty in demonstrating that many were in fact typhoid fever. The causative organism was Type C. After a period of rehabilitation in Persia these Poles were transferred westwards, mainly to Palestine.

In the summer months of 1942 an outbreak of typhoid fever of some magnitude spread through Palestine and Syria. From the Public Health Laboratories, Jerusalem, representative batches of cultures emanating from hospitals in Haifa, the Tel-Aviv/Jaffa area, and Jerusalem itself were sent for typing. Without exception all were Type C. Another batch, which also proved to be Type C, was received from the Bacteriology Department of the American University at Beirut. It is doubtful if this particular strain ever made its way across the Sinai desert. Although sporadic cases caused by Type C occurred among the troops in Egypt, and one large outbreak took place in an R.A.F. unit, it is more likely that these were related to the prisoner-of-war outbreak already mentioned.

For the first time Type D became comparatively common in Egypt. Early in 1941 a small group of four cases occurred in an R.A.F. unit, and later two cases were found

*Not now listed under this designation.

in a New Zealand regiment. The majority of, though not all, the Type D infections which appeared subsequently were either in the R.A.F. or in New Zealand troops.

The Final Phase

The next and final phase followed the Battle of Alamein. As our armies moved forward and Mersa Matruh was recaptured, we found that the Axis troops had used the Egyptian barracks there as a hospital, and that in this hospital were a large number of seriously ill men, both German and Italian, most of whom were suffering from typhoid fever. The organism with which they were infected was Type A, and from these patients and subsequent cases which occurred among the prisoners captured at the time a large number of cultures of this type reached me. This outbreak was soon checked and did not spread in the prisoner-of-war camps, among our troops, or in the civilian population. I might say that, with our previous experience in mind, all these new prisoners were promptly vaccinated with British Army vaccine.

It would be a mistake to imply that the information gained from typing these strains was of much practical value to the epidemiologists. The steady inflow of unseasoned and inexperienced troops into the Force, the constant movement of troops within the area, and the need to make the utmost use of man-power, which led to the employment of prisoners of war and civilians in duties connected with the handling of food, made the tracking down and eliminating of carriers a task of impossible magnitude. The entire available laboratory resources, directed to this subject alone, would have done little more than touch the fringe of it. The problem had to be tackled in other ways, and the fact that the incidence of enteric group fevers in the British Army in the Middle East for the years 1942 and 1943 was 0.8 per 1,000, a figure which compares favourably with the pre-war level, is evidence that these measures were reasonably successful. Nevertheless, the information which accrued from the typing results was of general interest and gave very clear evidence of the usefulness of this method in maintaining a check on the spread of infection.

An Unsolved Problem

A brief account of a problem which was revealed, though not solved, by phage-typing will round off this tale. In 1943 occasional sporadic cases of typhoid fever occurred among R.A.F. personnel—the figures are lost, but my recollection is that there were between 12 and 20. Without exception these were Type G, which at that time was not much in evidence elsewhere. The curious feature of this observation was that these cases were widely scattered throughout the command, one coming from as far afield as Malta. A special effort was made to discover the source of this infection, and the surprising fact emerged that, except for odd groups of two or three, these cases had no apparent association with each other, and were separated by distances which excluded all the more familiar channels of infection. The problem, so far as I am aware, remains unsolved. Our guess was that infection might be coming from a carrier at home who was engaged in making up and dispatching parcels of "comforts," but this was never confirmed. There can be little doubt that these cases did have a common source, which would never have been suspected had it not been for the phage-typing results. In less difficult circumstances it is possible that the carrier would have been tracked down and the danger of further infection from this source eliminated.

Paratyphoid Fever

Fever caused by *Salm. paratyphi* B is a serious problem in this and certain other countries, being much commoner than typhoid fever. The application of phage-typing follows the same lines and may provide an extremely useful label by which the relationship of cases and carriers can be checked.

A good example is furnished by an outbreak which occurred in Wootton, Isle of Wight, and has been reported by Wallace and Mackenzie (1947). In all, 62 persons were affected, including members of the family of the farmer who supplied milk to the village. However, although the infection was undoubtedly milk-borne, the farmer's relatives were fellow sufferers and not the cause of the trouble. All the organisms isolated were of Vi phage Type I. The source was ultimately traced to two carriers in a distant house, whence the infection passed via a cesspool (flooded by heavy rain) and a stream to a muddy field on which the cows grazed. Conditions in the farm were somewhat primitive, and it appears that the milk became contaminated from infected mud on the cows. *Salm. paratyphi* B, Vi phage Type I, was isolated from the carriers and from various points along the channel of infection—the cesspool, the stream at various points, and the mud. It is true that most epidemiologists would regard the isolation of the causative organism at these points as sufficient evidence, but the confirmation given by phage-typing clinched the matter in a very convincing way.

Salmonella Typhi-murium

Up to date little has been done in the way of typing *Salm. typhi-murium*, although there are instances on record where, in the case of an outbreak of food-poisoning, the test performed by the Vi-phage method of Felix has been useful in confirming that the strains isolated from the patients and the suspected food were identical. It has been stated that the possible sources of infection with this organism are so numerous and heterogeneous that typing does not offer much assistance to the epidemiologist. It is doubtful if this is a valid criticism.

During the last two years most of the cultures isolated in the Manchester area have been typed by the direct method which has already been described. Now that the reliability of this method has been established it is possible to draw conclusions which would not previously have been justifiable. In one hospital ward sporadic infection without an explosive outbreak has been occurring for over a year. Sixty-two strains were isolated in 1951, and all were of the same "mark." The majority were from infants or young children in hospital or recently discharged, but some were from secondary cases among associates outside hospital, and eight were excreters among home contacts. The typing results were 100% consistent. It was felt by those concerned that without this evidence it would have been difficult to accept this large and disjointed series of infections as associated cases. The origin of the outbreak is shrouded in mystery, but the subsequent transmission seems to have been by a chain of cross-infections from convalescents and excreters kept in hospital for the treatment of their primary disease. Over 30 further cases have occurred in 1952.

An outbreak due to a different "mark" occurred and died out in this same hospital in 1950, but not before infection had been transferred to another hospital. In 1951 10 cross-infections with this "mark" occurred in a cubicle ward in the second hospital.

During a period of four weeks a total of 14 sporadic cases, three fatal, due to yet another "mark," occurred in the general population of the city. No connexion was established between these cases, but there is little reasonable doubt that the infection came from a common source.

The epidemiological picture in *Salm. typhi-murium* infection is of course complicated by the fact that this organism has a wide host range, being found in many animals, such as cattle, horses, dogs, rats and mice, hens, turkeys, and ducks. It can occur in a variety of foodstuffs, and it is possible that a comprehensive investigation might reveal an association between phage types and foods which would give some direction to epidemiological investigations. It seems probable that the typing of *Salm. typhi-murium* will assume greater importance in the future than it has in the past.

Other Salmonella Infections

Other varieties of *Salmonella* have been typed by O phages. *Salm. thompson*, for example, has been split up in this way into 11 types (Williams Smith, 1951). A large number—perhaps all—of the strains of this organism are lysogenic, and it seems likely that they could be accurately typed by the direct method—that is, by the identification of the symbiotic phage. *Salm. dublin* and *Salm. enteritidis* have been divided into six and eight types respectively (Lilleengen, 1950). There can be no doubt that, should occasion arise, any strain of *Salmonella* which became of economic importance could be typed by either O phages or by the direct method of symbiotic phage identification. These organisms are, of course, chiefly of interest to the veterinarian.

Dysentery

Some years ago an attempt was made to classify the mannitol-fermenting dysentery bacilli by means of phage-typing. This did not materialize as a practical routine procedure, mainly because it offered no advantage over the established serological method of identifying these organisms by their antigenic structure. It is doubtful if the epidemiological problems presented by infection with these organisms would be simplified by the additional breakdown which phage-typing might provide.

These remarks do not apply to *Shigella sonnei*, which has been a bugbear to the public health authorities in this country for many years. Various attempts have been made to work out a typing scheme for this organism. Hammarström (1949) has given this subject much attention and has produced a tentative scheme in which he uses 11 phages and recognizes 31 types of bacteria: actually he found 68, but regards 37 of these as unverified. It is clear from his reported results that there is a good deal of instability in the phage strains he used, and the very large number of types which he has found casts some doubt on the value of the method. Attempts at typing in this country have not progressed far. Cooper and Mayr-Harting (1951) found seven types in Bristol. They point out that the "multiplicity of types and the smallness of the epidemiological unit will make it possible to trace some of the strands in the tangle of the pathways of infection." Nevertheless, they express caution regarding the stability of the types. Much work is still needed on this subject, and so far little of practical value has emerged.

Cholera

Although a great deal of work was done in India on the bacteriophages of the cholera vibrio, no phage-typing scheme has been worked out in conformity with modern ideas. Bruce White (1937) observed that a particular "lysogenic" phage is present in most Indian strains of vibrio. Japanese and Chinese strains do not contain this phage but are lysed by it. El Tor and other non-pathogenic vibrios neither contain this phage nor are lysed by it.

Staphylococcal Infection

In staphylococcal infections, typing has proved of much assistance in tracking down carriers. It has been particularly useful in maternity wards, where, for example, outbreaks of pemphigus among newly born children may cause trouble. Several instances are now on record where, by typing the staphylococci recovered from the infants and those from nasal swabs taken from the staff of the institution, the carrier has been located and the outbreak terminated. Similar helpful results have been obtained in investigating outbreaks of mammary abscess. Staphylococci can, of course, be recovered from most nasal swabs. Without the more precise information given by phage-typing it would be impossible to pick out the carrier of the pathogenic strain from among those harbouring non-virulent cocci.

Cows often suffer from staphylococcal mastitis. Williams Smith (1948) made an extensive survey of this subject from the veterinary angle and found that 93.3% of the strains which he isolated could be typed by Wilson's phages. Although his findings did not enable him to differentiate strains which were either pathogenic or harmless so far as the cow was concerned, he made the important observation that types which have been shown to be accountable for human mastitis and food-poisoning have been found as causes of bovine mastitis, and can maintain themselves in the cow's udder for as long as six weeks. Raw milk from an infected but symptomless cow is therefore a potential source of human disease. Macdonald (1946) found *Staph. aureus* in more than 50% of samples of accredited milk, the majority belonging to a phage type commonly found in human infections. Strangely enough, practically all staphylococci isolated from the udders of sheep are different from those found in human beings.

Phage-typing has proved a useful tool for investigating outbreaks of staphylococcal food-poisoning and serves to link up the strains found in the patients, the contaminated food, and the source. A small outbreak reported by Gillespie (1947) is a typical example. A specific phage type of *Staph. aureus* was isolated from the faeces of five out of six cases of gastro-enteritis. The same type was *not* isolated from the noses of the six patients or from two food-handlers, but was found in the nose of the chef. Unfortunately, none of the trifle believed to have been the vehicle of transmission was available for culture.

Miscellaneous

Although, as already mentioned, a scheme has been suggested for typing *Pseudomonas pyocyanea*, nothing of any practical application has so far been published thereon. No workable scheme for typing streptococci has yet been devised. Unsuccessful attempts have been made by Williams Smith (1949) to isolate phages from brucella.

It is strange that no serious attempt has yet been made to evolve a scheme for typing diphtheria bacilli. Keogh, Simmons, and Anderson (1938) have pointed out that phage can be used as an auxiliary means of classification of strains of diphtheria bacilli, and have been able to show differences in gravis, mitis, and intermediate strains by this method. Recent work in Canada by Toshach (1950) suggests that adapted strains of phage for the diphtheria bacillus can be produced. A remarkable observation which is not altogether irrelevant is reported by Freeman (1951), who found that with a certain phage he could produce from non-virulent strains of *Corynebacterium diphtheriae* both a lysate containing potent toxin and symbiotically infected bacilli which were highly virulent and multiplied in this state indefinitely. The problems of the diphtheria bacillus and its related phages are without doubt ripe for careful investigation.

Conclusion

I have said enough to show that phage-typing has placed at the disposal of the epidemiologist a new and promising means of solving many of his problems, and that results of much importance and interest have already emerged from its use. I mean no disparagement of the work which has already been done when I say that a great deal has still to be learnt, both about the principles and the technology of typing and about the different ways in which it can be applied to the solution of epidemiological conundrums. This is a field of research which offers a very promising prospect.

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SAFETY-BELTS ARE NOT DANGEROUS

BY

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For the past ten years Crash Injury Research at Cornell Medical College, in New York City, has been analysing the causes of injuries in aeroplane accidents. Under the direction of Hugh De Haven, particular attention is paid to seat belts, and medical data from hundreds of crashes show that injury from safety-belts is rare. As a result seats and belts have been strengthened in military and civilian planes. The use of shoulder harness is advocated, but when this is not available pilots and passengers are encouraged to fasten their seat belts tightly. The Cornell project has been in close touch with the authorities in Great Britain, and its work has been well summarized in a recent article by Walter Tye (1952).

The U.S. programme was going well until the appearance in this *Journal* of a report on the Viking crash by Dr. Donald Teare (1951), who stated as one of his conclusions, "The immediate cause of death in more than half of the victims was acute flexion of the body over the safety-belt." The acceptance of this conclusion was immediate and its effects were widespread, at least in America. Several journals gave it prominence. The *Scientific American* in December, 1951, headed its abstract "The Dangerous Safety-Belt." Thousands of airline passengers became apprehensive and fastened their belts loosely if at all.

Results of Research

When Cornell's Crash Injury Research was started in 1942 it was popularly believed that 1,000-lb. (454-kg.) safety-belts caused internal injuries, and even cut people in two. Since that time a careful analysis of accident details and medical data in 858 crashes has shown that there is no foundation for such beliefs. The portions of the body adjacent to and supported by the safety-belt sustain less injury than any other body area. Also, the concept of acute flexion of the spine has proved to be untenable. When the body, held at the hips by a properly applied belt, is suddenly stopped there is immediate acute pivoting at the hips. The torso and the legs hinge on the safety-belt and jack-knife forward.

The 1,000-lb. belts formerly used in United States civil aircraft often broke, and now the minimum requirement for civil aircraft demands safety-belts with a holding capacity of 3,000 lb. (1,360 kg.). Careful analyses of several recent severe accidents in civil transports have shown bruises on the hips, but no evidence of serious flexion or belt injury.

The effect of seat belts was carefully studied in Germany during the war by Ruff (1941). With seat belts properly applied, just as they are now in British and American planes, he tested men in a swing that was stopped abruptly. The speed was increased gradually until the braking produced a maximum snubbing effect of 1,000 kg. (2,204 lb., about 14 G). He found that when the brake is applied the body goes through a pivoting movement with the belt as an axis. The body and head fly forward and downward, the legs forward and up. Ruff says, "The demands on the tissues and organs in the region of the belt were found to be entirely tolerable; in Test 7 a slight nausea occurred which lasted about an hour."

Cornell's Crash Injury Research has recently made a survey of 800 survivors in serious crashes in which the occupants were wearing seat belts. The belts were stronger than those in the Viking crash, most having a holding capacity of 2,000 lb. (907 kg.). There were 704 survivors with injuries in the head, 641 with injuries in the legs, and 250 with injuries in the combined areas of the lumbar spine, abdomen, hips, pelvis, sacrum, and perineum. However, injuries in the region of the belt (usually bruises) were sustained by a mere 32 survivors, and evidence of intra-abdominal injury was found among only 23 of the 800 survivors. Injuries from belts played a minor part in these crashes, in which exposure to belt injury was great because the belts were strong. It is not the belt that causes injury if the body jerks forward and strikes dangerous objects in the plane. Little evidence regarding belt injury can be obtained in severe crashes when the belt or its attachments break, allowing the victim to shoot forward into a mass of wreckage.

Analysis of the Viking Crash

With this background we are in a position to study the evidence presented in the Viking crash. Dr. Teare's article is important, as it represents one of the most comprehensive and careful studies of pathological findings in a severe accident. In his brief report he could not make the type of analysis that is employed by the Crash Injury Research investigators, and it is doubtful if he could anticipate the effect of his conclusions. Fortunately, analysis is now possible, since we have received a map of the landing-field showing the location of parts of the plane, photographs of the wreckage, and details of the necropsies of the 28 victims. We hope that Dr. Teare will forgive us if we differ from his conclusions.

The basic facts of the case are derived from evidence on the ground and in the wreckage. On October 31, 1950, the Viking aircraft crashed in a thick fog at London Airport. There were no witnesses; the stewardess and the one passenger who survived have no accurate recollections. Both were seated in the rear of the cabin. There were marks at the edge of the runway indicating that the craft hit the ground at an angle of about 20 degrees and a speed of 120 knots as judged from scars left by the propellers, though some estimates are as low as 80 knots. The plane bounced and then was airborne for about half a mile (800 metres), possibly out of control, before it struck the edge of a concrete runway with the right wing while flying in a right-wing-low attitude. The right wing was crushed and sheared off just outboard of the engine. The right tail plane and elevator (stabilizer) were also found in this vicinity. The ship cartwheeled, bounced, or slid 350 ft. (107 metres), hit a pile of "asbestos type" water-pipes, and came to a sliding stop. The aircraft caught fire; structures and bodies were badly burned and much evidence was destroyed.

The nature of the crash has an important bearing on the causes of the injuries. The first glancing impact could have caused little strain on the belts. The second and principal crash impact on the right wing must have thrown the

passengers heavily to the right side. Dr. A. Buchanan Barbour (1951), Chief Medical Officer of British European Airways, points out that the main force was towards the lateral aspect. The arm-rests of the chairs, being higher and more rigid than the lapstraps, may have been responsible for some of the intrathoracic, liver, and spleen injuries. It is impossible to say just when the seats broke loose, but they were stressed against almost 12 times gravity (11.7 G) in a forward direction and considerably less, approximately 5.85 G, laterally.

After this second impact there was much tumbling of the victims and the contents of the plane, with a final sliding impact against the pipes. At no time could there have been a great force from the belts themselves, since they had only a holding capacity of approximately 1,300 lb. (590 kg.), or about 7.6 G.

The Injuries

In our opinion the injuries are typical of those in severe crashes in which seats or safety-belt anchorages fail. Dr. Barbour, who visited the scene of the accident within an hour of its occurrence, says in his letter that he marvels that any living being, however seated, could have escaped from such total destruction. He points out that there were six passengers in aft-facing seats, all killed. The two survivors in the rear of the plane were sitting in forward-facing seats, but were not wearing their lapstraps.

Dr. Teare states that he believes most of the victims were dead before the outbreak of fire and that the remainder, whose injuries were very severe, were unconscious and lived only for a matter of seconds in the fire. He gives a brief table of "actual causes of death." Further information can be obtained by grouping all the injuries noted in the necropsy reports.

Injuries Reported in the 28 Necropsies

Injuries	No. of Individuals	Remarks
Fractures of skull	13	Plus 1 doubtful
Haemorrhage in brain or on its surface	20	,, 2 ,,
Fractures of spine at C 1, 2; D 3, 6, 8, 12; L 2	7	
Rupture of aorta ascribed to puncture by ribs or vertebra, at D 4, 4, 6, 6, 8, 12; L 2	7	
Rupture of aorta without fracture	1	
Fracture of ribs	17	Total fractures 155: ribs 1–6 115; ribs 7–12, 40
Injuries to lungs	23	
,, ,, heart	13	
Ruptures of liver	15	
,, ,, kidneys	10	
,, ,, spleen	10	
Fractures of sternum	4	
,, ,, extremities	16	25 fractures, plus 7 doubtful
,, ,, pelvis	8	
"Bursting of abdomen"	1	Due to burns
Injuries to stomach and intestines	0	
,, ,, pelvic contents	0	

The distribution of injuries in the Viking crash corresponds well with that found by the Crash Injury Research group in their study of severe crashes. Damage was least in the region held by the belt. All 28 victims had injuries to the head or upper thorax; 21 had injuries to the lower thorax, liver, spleen, or kidneys; 7 had fractures of the pelvis, but 6 of these showed multiple fractures in the upper part of the body. In one woman, badly burnt, there was "bursting of the abdomen" along with great destruction of the head and body. In all cases the stomach, intestines, and pelvic contents were intact.

Dr. Teare says, "The ruptures of the aorta were associated with fractures of the ribs, disruption of the intercostal muscles, fractures of the spine, or laceration and bruising of the anterior surface of the liver." These injuries were, in Dr. Teare's opinion, caused by "acute flexion of the body over the safety-belt." It is difficult to see how the spine could have been flexed any more acutely in this accident than in a wrestling match or football game unless the body were hurled free, striking some hard object. Dr. P. S. Rutherford (1951) reports four cases of rupture of the aorta which he ascribes to a downward pull of the viscera. Three of these were in automobile accidents and one in a man who fell from a roof and landed on his feet.

Dr. Milton Helpern, Deputy Chief Medical Examiner for the City of New York, has been kind enough to go over the data with me. In his experience, rupture of the aorta is quite common in automobile accidents and falls from heights. For example, in New York in the year 1950 there were 15 victims of automobile accidents and 3 victims of falls in whom rupture of the aorta was given as a cause of death, to say nothing of many more cases in which it accompanied other causes of death. While reviewing Dr. Teare's findings, Dr. Helpern commented on the fact that no ruptures of the stomach, intestines, or bladder were found in the Viking disaster, yet these are frequent when the abdomen is injured. He saw no signs of damage from seat belts.

Summary

A report in the *British Medical Journal* of the Viking crash presented the conclusion that "the immediate cause of death in more than half of the victims was acute flexion of the body over the safety-belt." This report on one crash has been quoted extensively in America and has caused apprehension about the use of safety-belts by airline passengers.

Analysis of the crash conditions in the Viking crash, and of the 28 necropsies, indicates that seats and safety-belt anchorages broke, except in the case of the two survivors (who were not wearing their belts). Among the victims there was a great predominance of fractures of the head and upper part of the body. There were fewest injuries in the region of the seat belt. There is no proof that any of the injuries were due to belts.

Analysis of 858 crashes made by the Cornell Crash Injury Research project provides evidence that injuries from seat-belts are rare, even with belts and attachments much stronger than those used in the Viking.

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When visiting the Staffordshire coalfield this week the Minister of Fuel and Power declared that he was anxious to introduce a new Safety in the Mines Bill. That more attention should be given to this subject is evident to anyone reading the recent report of the Inspector of Mines for the North-western Division, Mr. G. Hoyle (H.M.S.O., 1s. 6d.). "I make no excuse," he says, "for repeating what I have said before, that among the former things which must pass away with the reshaping of the pits is the attitude that so many accidents in mines are inevitable. . . . It should be realized that many of the accidents occurring now are caused in the same way as accidents were caused 50 years ago and that *the remedy in many cases is known.*" During 1951 in the North-western Division alone there were 23 fatal accidents, 2 less than in 1950, but reportable non-fatal accidents had risen from 152 to 173. Even more disturbing is the attitude revealed to dust suppression. "General progress in the suppression of dust has been disappointing, and at many pits there appears to be a lack of urgency on the part of both officials and workmen in dealing with this problem." Figures for 1951 show no improvement during the year in the proportion of faces in the division (62%) classed as dusty. Mr. Hoyle also reports that at a few pits there is deliberate opposition to dust-laying, shown "by the regular damaging of dust-suppression fittings."

ANTAGONISM OF ANTICOAGULANTS DICOUMAROL, TROMEXAN, AND PHENYLINDANDIONE BY VITAMIN K_1

BY

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There are many conflicting opinions on the value of water-soluble preparations of vitamin K in overcoming prothrombin deficiency induced by dicoumarol. On the one hand, James *et al.* (1949) stated that water-soluble preparations (menadione (menaphthone *B.P.*) and "synkavit"), in large doses intravenously, had little effect in shortening the prothrombin time after dicoumarol therapy. Miller *et al.* (1950) came to the same conclusions.

On the other hand, in contrast to these reports, Overman and his associates (1951) found that water-soluble preparations of vitamin K were effective in overcoming the excessively prolonged prothrombin times encountered in dicoumarol therapy. In criticism of James's reports, Overman *et al.* state that the large amounts of dicoumarol given in James's experiments may have significantly altered the response to water-soluble vitamin K. In addition, they thought that the fact that in Miller's experiments the dicoumarol and vitamin K were administered simultaneously probably altered the response to the vitamin K.

In my experience water-soluble preparations of vitamin K, given in large doses of 200–600 mg. intravenously, have only a very limited effect in reducing the prothrombin times in patients receiving dicoumarol. Patients sensitive to dicoumarol will often have a sudden marked rise in the prothrombin time in the early days of treatment. In most of these the withholding of dicoumarol will result in a rapid fall in the prothrombin time. Administration of water-soluble vitamin K will in many cases hasten the fall in the prothrombin time, though this response is not always to be relied upon. In addition, I have found that water-soluble preparations will in many cases produce an appreciable fall in the prothrombin time in patients in whom dicoumarol has been stopped for several days, provided that the initial doses of dicoumarol were not excessive. I believe that the water-soluble preparations of vitamin K are effective only when most of the dicoumarol has already been excreted. This is supported by Overman's experiments, in which the average dose of dicoumarol was only 403 mg. and in half of the cases no dicoumarol had been given in the 48 hours before the administration of water-soluble vitamin K. In those cases in which dicoumarol was given in the 24 hours preceding the administration of vitamin K, the prothrombin time (when it was stated) rose suddenly from a therapeutically safe level to a dangerously high level within 24 hours. This sudden rise in 24 hours after small or average doses of dicoumarol represents the reaction of the sensitive patient who will often respond to the withholding of dicoumarol alone. In the one case in Overman's series in which the prothrombin level was below 10% of normal on two successive days, and in which dicoumarol had been given within the 24 hours before the administration of vitamin K, there was no response to water-soluble vitamin K.

Vitamin K_1

In contrast to the lack of response to water-soluble preparations of vitamin K, both James and Miller noted an effective response to intravenous doses of 500 mg. of vitamin K_1 oxide and vitamin K_1. Miller found that vitamin K_1 was more effective than vitamin K_1 oxide. In a more recent report, Fuller and Barker (1951) concluded that an oral dose of 500 mg. of vitamin K_1 was a satisfactory dicoumarol antagonist, significantly reducing the prothrombin time 20 hours after the administration of vitamin K_1.

To assess the value of vitamin K_1, given orally, 500 mg. was administered to seven patients on dicoumarol, four patients on "tromexan," and seven patients on the more recently introduced anticoagulant phenylindandione. (This last drug has an effect midway between that of dicoumarol and that of tromexan.) In nearly all the cases, average or large doses of the anticoagulant drugs were given to produce a severe prothrombin deficiency in the region of 10% or below on at least two successive days (Case 3 is the one exception). With the thromboplastin used in this study, prothrombin times of 35 seconds and 50 seconds represent prothrombin levels of 20% and 10% of normal respectively. Six cases of the series (5, 7, 13, 14, 17, and 18) had severe

TABLE I.—*Response to 500 mg. Vitamin K_1 Orally in Patients on Dicoumarol*

Case	Age		K Day −2	K Day −1	K Day	Prothrombin Times—Hours after K_1					Expected P.T. at 20 hrs.	Hours between Last Dose of Dicoumarol and Vit. K_1	Total Dicoumarol Given
						4 hrs.	6 hrs.	8 hrs.	12 hrs.	20 hrs.			
1	68	P.T.	—	70	85	—	—	14		15	70–85	24	550 mg. in 3 days
		D. mg.	200	50									
		K_1 mg.	—	—	500 haematuria								
2	68	P.T.	58	60	60		20		18		50–60	23	600 mg. in 7 days
		D.	—	50	—								
		K_1	—	—	500								
3	56	P.T.	—	—	110	54		23		19	110+	6	800 mg. in 2 days
		D.	200	600	—								
		K_1	—	—	500								
4	64	P.T.	—	58	65			21		18	80–100	½	850 mg. in 6 days
		D.	50	50	100								
		K_1	—	—	500								
5	72	P.T.	70	120	160	120			47	26	120+	19	800 mg. in 5 days
		D.	200	50	—								
		K_1	—	—	500 haemorrhage								
6	60	P.T.	43	44	65	40		21		16	65	1	1,200 mg. in 8 days
		D.	100	150	100								
		K_1	—	—	500								
7	58	P.T.	80	75	100		59	28		16	120+	8	1,850 mg. in 11 days
		D.	200	200	100								
		K_1	—	—	500								

P.T.=Prothrombin time in seconds. D.=Dicoumarol. Expected P.T.=Approximate expected prothrombin time if no K_1 had been given.

TABLE II.—*Response to 500 mg. Vitamin K_1 Orally in Patients on Phenylindandione (P.I.D.)*

Case	Age		K Day −2	K Day −1	K Day	Prothrombin Times—Hours After K_1 4 hrs.	6 hrs.	8 hrs.	12 hrs.	20 hrs.	Expected P.T. at 20 hrs.	Hours Between Last Dose of P.I.D. and K_1	Total P.I.D. Given
8	63	P.T.	—	45	50	34		19		18	50	1	1,650 mg. in 15 days
		P.I.D. mg.	100	100	100								
		K_1 mg.	—	—	500								
9	70	P.T.	34	44	52	32	23			18	30–35	16	1,250 mg. in 10 days
		P.I.D.	150	200	—								
		K_1	—	—	500								
10	71	P.T.	—	48	58	44		21		20	50	1	1,550 mg. in 15 days
		P.I.D.	100	150	50								
		K_1	—	—	500								
11	85	P.T.	58	60	85	31		23		22	75–85	2	1,400 mg. in 9 days
		P.I.D.	150	200	100								
		K_1	—	—	500								
12	86	P.T.	55	60	93	55		27		14	95+	4	1,150 mg. in 6 days
		P.I.D.	150	200	200								
		K_1	—	—	500								
13	61	P.T.	72	90	110	80	31	22	22	21	100+	5	1,150 mg. in 6 days
		P.I.D.	200	200	50								
		K_1	—	—	500								
					haematuria								
14	86	P.T.	85	110	120	150	47	43	33	23	120+	10	1,700 mg. in 8 days
		P.I.D.	200	250	—								
		K_1	—	—	500								

P.T. = Prothrombin time in seconds. Expected P.T. = Approximate expected prothrombin time if no K_1 had been given.

TABLE III.—*Response to 500 mg. Vitamin K_1 Orally in Patients on Tromexan*

Case	Age		K Day −2	K Day −1	K Day	Prothrombin Times—Hours After K_1 4 hrs.	6 hrs.	8 hrs.	12 hrs.	20 hrs.	Expected P.T. at 20 hrs.	Hours Between Last Dose of Tromexan and K_1	Total Tromexan Given
15	62	P.T.	—	55	62			30		20	50–60	1	4,800 mg. in 15 days
		T. mg.	—	300	300								
		K_1	—	—	500								
16	64	P.T.	47	57	66	26		19		17	60–70	1	4,800 mg. in 6 days
		T.	900	900	900								
		K_1	—	—	500								
17	53	P.T.	60	95	115	75		24		17	80–90	6	6,300 mg. in 6 days
		T.	900	1,200	300								
		K_1	—	—	500								
18	61	P.T.	67	95	95	80		22		14	65–80	6	5,700 mg. in 6 days
		T.	900	900	300								
		K_1	—	—	500								
					haematuria epistaxis								

P.T. = Prothrombin time in seconds. T. = Tromexan. Expected P.T. = Approximate expected prothrombin time if no K_1 had been given.

prothrombin deficiencies, with times of 75 seconds and over on at least two successive days. In three cases (5, 13, and 18) anticoagulant drugs were persisted with in order to produce haemorrhage, and, in addition, microscopical haematuria was noted in a further case (Case 1).

To eliminate any appreciable fall that might result merely from stopping anticoagulant drugs, all the cases had the last doses of the anticoagulant less than 24 hours before receiving vitamin K_1. In 14 of the 18 cases the longest interval between the administration of anticoagulants and vitamin K_1 was 10 hours, with an average of 3½ hours.

Tables I to III show the responses to oral vitamin K_1 in these 18 patients. In all cases the prothrombin time fell to a safe level within eight hours, and if in each case the prothrombin time had been taken six hours after vitamin K_1 had been given it would probably have been found that a safe prothrombin level of above 10% had been reached in six hours in nearly all. (One exception is Case 7, in which the prothrombin time was 59 seconds at six hours, representing a level of approximately just below 10%.) The prothrombin times in all cases had fallen to 26 seconds or below within 20 hours.

Fig. 1 shows the dramatic response to vitamin K_1 in the four most severe cases, including the three in which frank haemorrhage occurred.

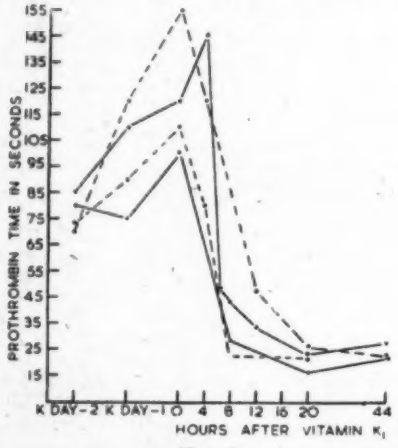

FIG. 1

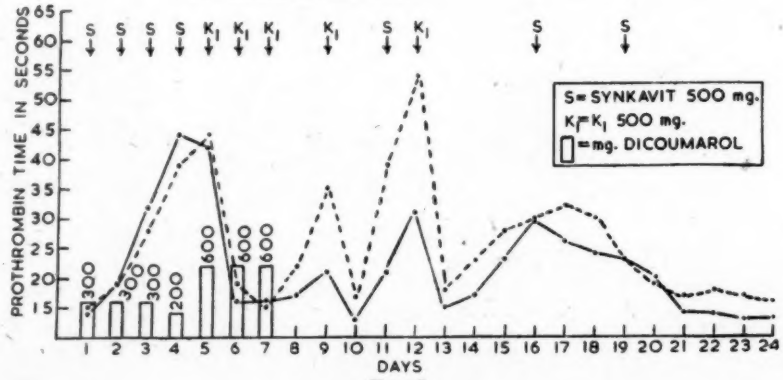

FIG. 2

FIG. 1.—The response to 500 mg. of vitamin K_1 given orally, in four cases with severe prothrombin deficiencies, including frank haemorrhages in three cases. FIG. 2.—Shows the superiority of vitamin K_1 compared with water-soluble vitamin K (synkavit) in counteracting the prothrombopenic action of large doses of dicoumarol in two cases.

In two cases (7 and 14) a "rebound phenomenon" occurred. In Case 7 very large doses of dicoumarol had been given in the three or four days before vitamin K_1 was administered, and a prothrombin level of below 10% of normal was present on three days. After, however, the prothrombin time had fallen to normal (16 seconds) within 20 hours of the administration of vitamin K_1, it gradually rose to 22, 29, and 36 seconds in the next three days. A further dose of 500 mg. of vitamin K_1, orally, restored the prothrombin time to normal, with no further rise. Similarly, in Case 14, after excessive doses of phenylindandione, resulting in a prothrombin level of well below 10% of normal for three days before vitamin K_1 was given, the prothrombin time fell to 23 seconds (a level of approximately 40%) within 20 hours, only to rise again to 27 and 31 seconds in the next two days. One further dose of 500 mg. of vitamin K_1 was sufficient to restore and maintain the prothrombin time at normal.

Comparison Between Water-soluble Vitamin K and Vitamin K_1

To assess the relative effects of water-soluble vitamin K and vitamin K_1 the following experiments were carried out (see Fig. 2). 1,100 mg. of dicoumarol was given to each of two cases over a period of four days. At the same time 500 mg. of synkavit (a water-soluble preparation of vitamin K) was given daily in two doses of 250 mg. intramuscularly. (Owing to the toxic reactions it was not possible to give such large doses of synkavit intravenously.) As can be seen from Fig. 2, the simultaneous administration of synkavit and dicoumarol did not prevent the prothrombopenic effect (although there is no doubt that the synkavit had some antagonistic effect, as without that substance one would have expected higher prothrombin times after such large doses of dicoumarol). On the fifth day 500 mg. of vitamin K_1 was given by mouth, and at the same time 600 mg. of dicoumarol (that is, double the dose given with synkavit). In 24 hours the prothrombin time had fallen from the region of 45 seconds to near normal—16 and 18 seconds. On each of the next two days 600 mg. of dicoumarol was given, with 500 mg. of vitamin K_1, and in spite of such large doses of dicoumarol the prothrombin times remained normal. In all, both cases had received 2,900 mg. of dicoumarol. On the eighth and ninth days the prothrombin times rose again, and a further 500 mg. of vitamin K_1 given on the ninth day once more restored the prothrombin times to normal by the following day. On the eleventh day the prothrombin times in both patients had risen again, and 500 mg. of synkavit failed to prevent the prothrombin time rising still higher on the twelfth day. A further dose of 500 mg. of vitamin K_1 on the twelfth day was needed to restore the rising prothrombin time to normal. It was not until 14 days after the last dose of dicoumarol that the prothrombin remained normal.

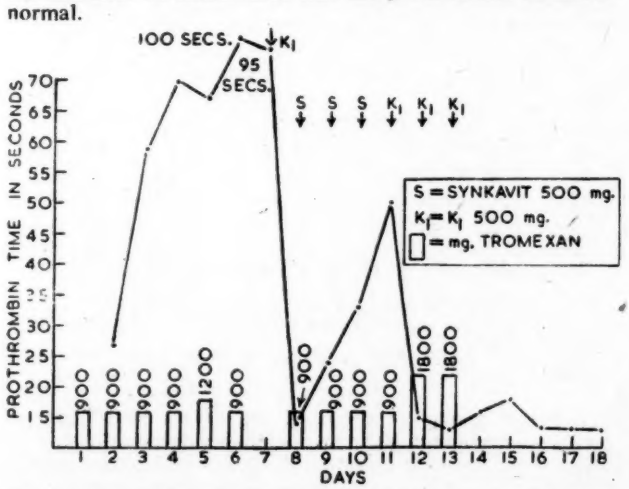

FIG. 3.—Shows the superiority of vitamin K_1 compared with water-soluble vitamin K (synkavit) in counteracting the prothrombopenic action of large doses of tromexan.

The above experiment shows the remarkable effect of vitamin K_1 in both preventing and counteracting the prothrombopenic effect of dicoumarol even after very large doses, whereas the water-soluble preparations of vitamin K had only a partial preventive effect. In addition, it shows the failure of water-soluble vitamin K to reduce the prothrombin time when any appreciable quantity of dicoumarol still remains in the body.

One further point can be noted from the above experiments. After very large doses of dicoumarol the drug may remain stored in the body for as long as 14 days. To overcome the effect of stored dicoumarol, repeated doses of vitamin K_1 are needed.

An experiment similar to the above was carried out in two patients when tromexan was used as the anticoagulant drug. Figs. 3 and 4 show the much greater effect of vitamin K_1 compared with that of water-soluble vitamin K. In contrast to the experiments with dicoumarol, no rebound phenomenon occurred, because tromexan is excreted so much more rapidly than dicoumarol. Unfortunately, supplies of the anticoagulant phenylindandione were insufficient to carry out similar experiments.

Conclusion

It is apparent that vitamin K_1 is most effective in overcoming the prothrombin deficiency induced by such drugs as dicoumarol, tromexan, and phenylindandione. Even with very severe deficiencies, resulting in prothrombin levels of below 10% for several days, an oral dose of 500 mg. of vitamin K_1 will restore the prothrombin time to a safe level within eight hours, the effect being evident within four hours. The effect was also noticed even when congestive failure was present.

In three cases with frank haemorrhagic manifestations vitamin K_1 stopped bleeding within a few hours, and no transfusions were necessary.

When very large doses of dicoumarol (and to a lesser extent phenylindandione) have been given, with the consequent storage of the drug in the body, repeated doses of vitamin K_1 may be needed to prevent a further rise in the prothrombin times—"rebound phenomenon." This effect does not occur with tromexan owing to the rapidity of excretion of the drug.

Comparison of the effect of water-soluble preparations of vitamin K with that of vitamin K_1 leaves no doubt that the latter should be the drug of choice when it is essential to overcome a severe prothrombin deficiency, particularly if bleeding is present. In the latter event, unless there are also signs of shock due to the lack of blood, it should not be necessary to resort to blood transfusions. The availability of vitamin K_1 should widen the scope of anticoagulant therapy with dicoumarol and allied drugs, so long as it is

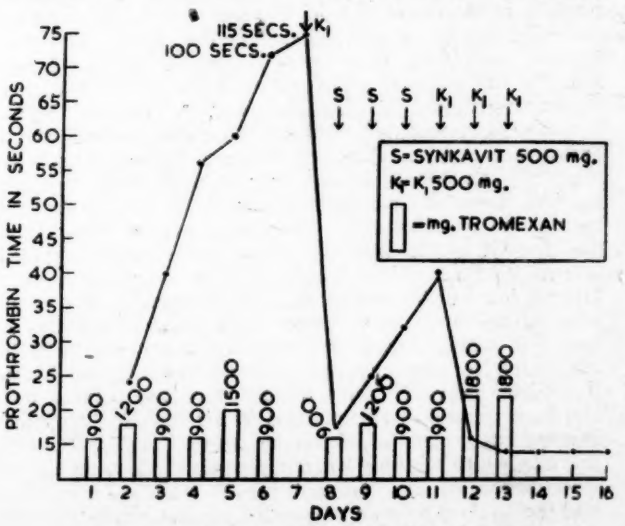

FIG. 4.—A similar experiment to that of Fig. 3.

remembered that prothrombin estimations are essential for their control. The possibility of an urgent operation being necessary in a patient on dicoumarol or allied drugs has always been a drawback to their use. This drawback is largely overcome by the use of vitamin K_1.

In considering the use of such a potent drug as vitamin K_1 it must be remembered that the prompt restoration of the prothrombin to a normal, or near normal, level in a patient requiring the use of anticoagulants will inevitably restore the dangers of thrombo-embolism. Vitamin K_1 must therefore be used with caution and only in cases where the danger of severe prothrombin deficiency overrides that of thrombo-embolism. This statement applies to the doses of vitamin K_1 used in this report. Further work is in progress with smaller doses of vitamin K_1, which it is hoped will overcome a dangerous prothrombin deficiency that may arise from anticoagulant therapy but will not restore the prothrombin to a level where thrombo-embolism is likely.

In using large doses of vitamin K_1 it must also be remembered that the patient may become refractory to anticoagulants and require much larger doses of the anticoagulant drug after the administration of the vitamin.

Summary

In 18 patients, vitamin K_1, in a single oral dose of 500 mg., was completely effective in restoring a safe prothrombin level after a severe and prolonged prothrombin deficiency due to such anticoagulant drugs as dicoumarol, tromexan, and phenylindandione.

This effect was evident within eight hours, and the action of the vitamin was apparent within four hours.

In three cases of frank haemorrhage due to anticoagulant drugs, an oral dose of vitamin K_1 was in itself sufficient to stop bleeding in a matter of hours.

I wish to thank Roche Products Ltd. for the generous supplies of the vitamin K_1 used in this work, and in particular Dr. F. Wrigley for his advice and help.

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Nation-wide hunts for donors of rare types of blood should no longer be necessary with the coming into use this week of a national panel of nearly 2,000 donors whose red blood cells have been classified down to the finest subdivisions of the blood groups. Several hundred distinguishable kinds of blood are included in the panel. The preliminary testing and selection of donors for the panel was done by the regional transfusion centres of the National Blood Transfusion Service, the Scottish National Blood Transfusion Association, and the Northern Ireland Blood Transfusion Service. The Blood Group Reference Laboratory, run on behalf of the Ministry of Health by the Medical Research Council, was responsible for the detailed testing and classification. The testing of the donors and the classifying and checking of the results have occupied several members of the laboratory staff for about a year. The register will be kept up to date by replacing any donor who resigns by a new donor. The regional transfusion centre in whose region the resigning donor lives will be responsible for replacing him, and the Blood Group Reference Laboratory will carry out the necessary detailed tests and issue periodical amendments to the register. No other country has a panel of donors in any way comparable with this one, which has only become possible through the unique organization of the National Blood Transfusion Services and the leading position which this country holds in blood-group research and technology.

STUDIES IN PRE-DIABETES

BY

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PART I

ITS INCIDENCE IN THE CAPE, ITS EARLY DETECTION, AND THE CONCEPT OF THE PRE-DIABETIC FATHER

Coming events cast their shadows before. The woman destined to develop diabetes divulges her future fate by producing infants which are dead,[1-7] or large,[1 3 7-11] by rapid obesity during pregnancy,[6 8 11 12] and perhaps by overlactation.[12] The only dissentient voice has been that of Herzstein and Dolger,[13] and their figures are of doubtful validity.[1]

Observations on Pre-diabetic Women

The high foetal loss rate and, particularly, the macroinfantia are applicable to pre-diabetic women in the Cape, both white and "coloured" (mixed race), and probably African also.

Method.—The method of personal questioning of unselected consecutive patients which was adopted is admittedly subject to great inaccuracy. For controls we took a series of cases of similar race and age distribution who were attending hospital for various reasons, none of them being known diabetics. As there is no reason to believe that diabetics are greater exaggerators of birth size than other hospital patients, conclusions drawn from a comparison of the two groups should be valid. Absolute figures, however, cannot be regarded as accurate. Babies are included in the survey only when the mothers knew their weight with reasonable and credible accuracy. "Large" was not considered good enough, nor "I'm sure he was over 10 lb.," unless the latter was confirmed by definite memory of the use of a scale and suitable remarks by doctor or midwife. Whenever a large baby was claimed every verbal effort was made to obtain confirmatory evidence before acceptance.

"Stillbirths" here include deaths within 48 hours of birth, and their recorded percentages are also subject to inaccuracies.

Large Babies

Table I shows that 62% of the women who develop overt diabetes after child-bearing claim to have had at least one baby over 10 lb. (4.5 kg.) in weight. This compares with

TABLE I.—*Pre-diabetic and Control Mothers*

	Total Mothers		Mothers with at Least 1 Child over 10 lb.		Mothers with No Child over 8 lb.		Mothers with at Least 1 Stillbirth	
	P.	C.	P.	C.	P.	C.	P.	C.
White ..	50	50	31	7	2	23	8	4
Coloured	50	50	31	5	6	30	22	9
Total	100	100*	62%	12%	8%	53%	30%†	13%†

P = Pre-diabetic. C. = Control.
* Total number of control mothers was actually 130—reduced to 100 for easy comparison.
† Difference between these two proportions is two and a half times its standard error.

Kriss and Futcher's[9] 58% and the figures of Miller[1] and Moss and Mulholland.[7] So commonly is there a story of several large babies, sometimes with stillbirths, that we have come to regard this as strongly confirmatory of diabetes in a doubtful new case, so that necessary treatment may be started without awaiting the results of chemical analyses.

TABLE II.—*Children of Pre-diabetic and Control Mothers*

	Total Children of		% Over 9 lb.		% Over 10 lb.		% Over 11 lb.		% Under 8 lb.		% Stillbirths	
	P.M.	C.M.	P.M.	C.M.	P.M.	C.M.	P.M.	C.M.	P.M.	C.M.	P.M.	C.M.
White ..	210	136	55%	17%	34%	7·4%	17·6%	2·2%	19%	72%	7·8%	3%
Coloured ..	218	303	40%	8·3%	28%	3·3%	11%	1%	25%	72%	21%	6·8%
Total ..	428	439	47%	11%	31%	4·6%	13%	1·4%	22%	72%	14%	8%

P.M. = Pre-diabetic mothers; C.M. = Control mothers.

Table II shows that 31% of babies of the pre-diabetic women (the women shown in Table I) were over 10 lb. (4.5 kg.), as against 4.6% of the control women's babies. This rate compares with that in several other series,[7 9 10] but is higher than most for reasons already considered. The high mean birth weight in the pre-diabetic period may be better appreciated from the fact that only 22% of the babies were under 8 lb. (3.6 kg.), as opposed to 72% in the control series.

The only pure negress who knew accurately her babies' birth weights had had two sets of twins in the 10-year period preceding the onset of clinical diabetes, both in hospital. The combined weights were 12 lb. (5.4 kg.) and 15 lb. (6.8 kg.). From this and other observations mentioned later it appears that the pre-diabetic state may apply to the African.

The actual birth weights of 1,000 children (500 white and 500 coloured) born in hospital were also recorded (Table III) to see how the proportion in the various groups differed

TABLE III.—*Birth Weights of Unselected Children in Hospital*

	Total	Under 8 lb.	8–9 lb.	9–10 lb.	Over 10 lb.
White	500	63%	25%	10%	2%
Coloured ..	500	86%	10%	4%	<1%
Total ..	1,000	75·5%	17·2%	6%	1·3%

from those calculated from questioning the mothers. In this way we hoped to get some idea of parents' "exaggerator rate." Actually the proportion in the comparable weight groups were very similar, except in the over 10 lb. group, with 4.6% of children by questioning and only 1.3% by records (the usual figure for 10-pounders[15–17]). This exaggeration of claimed 10-pounders demonstrates the necessity for our control series of mothers. Incidentally, Table III shows also the tendency for the coloured baby to be smaller on the whole than that of pure white stock (cf. Woodrow and Robertson[18]).

Stillbirths

Tables I and II also indicate that the stillbirth rate is higher in the pre-diabetic, the 14% of total babies comparing with several other reports,[2–5 7 10 14] whose figures vary from 10 to 25%, most of which are not, however, strictly comparable. Incidentally, the stillbirth rate in established diabetics in the Cape nears 50%.[19] It may be noted that both tables indicate a much higher stillbirth rate in coloured women than in white, both pre-diabetic and control, which may be related to environmental conditions.

Time Interval Before Development of Diabetes

It is often stated that the tendency to produce large babies and stillbirths is evident for 15 to 20 years before manifest diabetes develops. Table IV suggests that this tendency goes back indefinitely, so that there is still an excess of large babies and stillbirths more than 30 years before the onset of diabetes. Thus 26% of such babies were over 10 lb. (as against the 4.6% of the control series). The figures have not been subjected to statistical analysis from this angle because of their inherent inaccuracies, but they are certainly very suggestive, and compare with those of Kriss and Futcher[9] and of Moss and Mulholland.[7] One old but

TABLE IV.—*Length of Pre-diabetic Period*

	Total Babies	Babies over 10 lb.	Stillbirths
0–4 years before diabetes	35	54%	29%
5–9 " " "	55	44%	13%
10–14 " " "	61	23%	23%
15–19 " " "	92	28%	13%
20–29 " " "	102	35%	8%
30+ " " "	43	26%	9·3%
Control series	39%	33% (4·6%)	14% (5%)
Whole series			

intelligent woman claimed to have had an 11-lb. (5-kg.) baby 58 years before developing diabetes. As in other series,[1 7 11] the proportion of large babies and stillbirths rises as the onset of diabetes approaches.

Pre-diabetic Fathers

Discredited theories attributed large babies to maternal hyperglycaemia. Since then the work of Young[20] has established the identity of, or at least the close connexion between, the diabetogenic and growth factors of the anterior pituitary. An excessive anterior pituitary function, particularly with respect to this hormone, might therefore account both for the large babies and for the maternal diabetes,[1 9 11] and perhaps maternal obesity[5] and superlactation[13] as well. An extension of pituitary overactivity to the gonadotropic hormone might explain the high foetal death rate.[21] Wilder[22] objects that none of the usual manifestations of hypophysial overactivity are present in these cases. Moreover, the rather naive assumption that the mother is solely responsible for the child is tacitly understood. I am indebted to Professor G. C. Linder for suggesting that inquiry should be made to see whether *paternal* diabetes and pre-diabetes may not be associated with large babies and high foetal loss. In other words, why should there not be a genetic factor, linked with that for diabetes, which makes for these features? Why should they necessarily be conditioned solely by the *milieu intérieur* of the mother ("maternal environment")?

Method.—We have attempted, by the methods described above, to tackle this possibility by interviewing the men who attended our diabetic clinic. It was a prolonged task, since

TABLE V.—*Pre-diabetic Fathers and Control Fathers*

	Total	Fathers with at Least One Child over 9 lb	Fathers with at Least One Child Over 10 lb.	Fathers with at Least One Stillbirth
Pre-diabetic fathers ..	49	56%	35%	8%
Control fathers ..	50	14%	12%	8%
Difference	—	—	23	—
S.E. of difference ..	—	—	8·2	—
Difference/its S.E. ..	—	—	2·8	—

TABLE VI.—*Children of Pre-diabetic and Control Fathers*

	Total Children	Under 8 lb.	8–9 lb.	9–10 lb.	Over 10 lb.	Stillbirth Rate
Of pre-diabetic fathers ..	189	72 (38%)	69 (36·5%)	22 (11·7%)	*26 (14·1%)	3%
Of control fathers ..	147	88 (60%)	48 (32·6%)	3 (2·0%)	*8 (5·4%)	3%

$\chi^2 = 25·9$; d.f. = 3; $P << 0·01$.
* Difference between these two proportions is 2·7 times its standard error.

comparatively few knew their children's birth weights, and in addition we do not treat so many males at the clinic. Moreover, as this was a crucial experiment, we insisted on some sort of corroborative evidence. At the same time we obtained data from a comparable group of non-diabetic outpatient fathers as a control series in case it might be objected that to compare diabetic *males* with non-diabetic *females* was introducing a second variable. In fact, however, the data obtained in the male control series (Tables V and VI) were essentially the same as those in the female controls (Tables I and II), so that it would be legitimate to use both together as a control series.

Large Babies

When our figures were analysed we found to our surprise that there was in fact a high proportion of large birth weights among the children of diabetic men (Tables V and VI). Forty-nine fathers had 189 children, of whom 14% were said to be over 10 lb. (4.5 kg.) at birth, compared with 5% of the controls. Analysis of Table VI by two methods indicates that these birth-weight differences are highly significant. As in the stories of the women, some of these men gave an account of repeated large babies; one had all five over 10 lb., another had three out of four over 10 lb. It might be contended that such stories as these may have been due to pre-diabetic wives, but this is unlikely for various reasons. First, no similar histories were obtained in the control series; secondly, in two such fathers the youngest child was over 20 years old, yet the wife was still not diabetic; thirdly, one man had large babies by two wives; and, fourthly, the tolerance curve of one wife was quite normal.

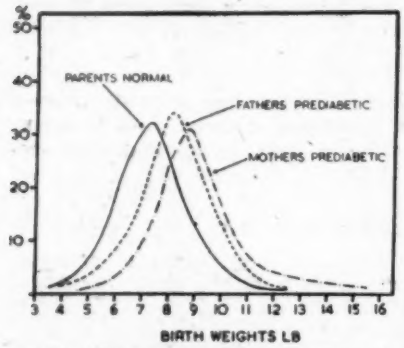

FIG. 1.—Frequency distribution curves of birth weights of babies born to normal parents, to pre-diabetic fathers, and to pre-diabetic mothers.

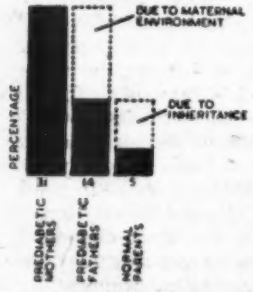

FIG. 2.—Comparison of proportion of infants over 10 lb. (4.5 kg.) born to pre-diabetic mothers, to pre-diabetic fathers, and to normal parents. Blocked differences show respectively the apparent importance of maternal internal environment and of inheritance in producing large babies.

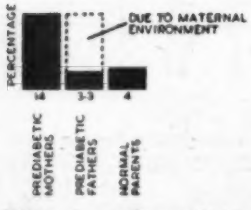

FIG. 3. — Comparison, similar to Fig. 2, of proportion of stillbirths born to pre-diabetic mothers, to pre-diabetic fathers, and to normal parents. The difference seems to be solely due to maternal environment.

Frequency distribution curves of birth weights (Fig. 1) demonstrate graphically the tendency of pre-diabetic mothers to produce large babies compared with the control series, while the curve for the babies of pre-diabetic fathers lies in between.

Interpretation

The stillbirth rate told quite another story—no difference between diabetic and control fathers. The evidence suggests, then, that the tendency to produce large babies is *partly* an inherited characteristic combined with a tendency to diabetes, passed on by the male as well as the female, and *partly* an effect of maternal environment as in the current hormonal hypothesis (Fig. 2). The excessive foetal loss, on the other hand, is entirely mediated by maternal factors (Fig. 3). Incidentally, the inherited factor must be autosomal, since about equal numbers of large girl and large boy babies are produced.

There is nothing inherently unlikely in this suggestion, no reason why large birth size should not be inherited, and some evidence that it is so inherited in *non-diabetic* families also.[9 12 28] Nevertheless, I do not claim that the present figures prove the existence of the pre-diabetic father syndrome, but it is hoped that further data from larger clinics may be able to substantiate or refute it.

EARLY DETECTION OF PRE-DIABETES AND "CHEMICAL DIABETES" IN MOTHERS

The recognition of the pre-diabetic state in retrospect by consideration of the obstetric history of a new diabetic patient may be of great theoretical importance, but can be of no value to the individuals directly concerned. We therefore decided to see whether, by means of a simple glucose-tolerance test on the sixth post-partum day, we could establish the presence of pre-diabetes or a mild diabetic state in women who gave birth to large babies in hospital. A curve at such a time is very largely reliable (see Part II).

Nearly 20 years ago Skipper[14] and White[6] suggested that mothers who have large babies should be examined for diabetes. This never appears to have been done on any scale, and at that time the significance of "pre-diabetes" was not realized, although Skipper seems to have been the first to notice that women may have large babies long before developing overt diabetes.

Kriss and Futcher[9] were able to predict that a mother of 23 having a first baby of over 10 lb. (4.5 kg.) had a 17.8% chance of becoming diabetic; but this did not help individual mothers, nor did it take account of *repeated* large babies or stillbirths.

Gilbert[11] approached the problem differently by examining the histories of 5,000 women confined some six years previously. Of these, he finally re-examined 21 who had had unexplained foetal losses or large babies, and found six to be diabetic, inasmuch as they had a raised tolerance curve.

Moss and Mulholland[7] found two patients without glycosuria who had given birth to several stillborn infants and who had diabetic tolerance curves.

Method.—All women confined in Groote Schuur Hospital (1949–50) whose babies weighed over 10 lb. were examined for glucose tolerance. Other mothers were sampled at random, so that their babies' weights fell into all groups. Most were tested on the sixth post-partum day, except that a few mothers of 10-pounders were sent to us from outside and were therefore rather later in the puerperium. None were known diabetics. Whenever possible all women who showed abnormal curves were re-examined six months later. No curve taken shortly after caesarean section is regarded as abnormal without repetition later. Altogether 165 parturient women have been tested, including 33 whose last baby weighed over 10 lb. and 14 whose babies were stillborn. A curve is called diabetic if either the two-hour level is over 140 mg. or the two-and-a-half-hour level over 130.

TABLE VII.—*Glucose-tolerance Curves in Parturient Mothers of Babies in Different Weight Groups*

	Last Baby Under 7 lb.	Last Baby 7–8½ lb.	Last Baby 8½–10 lb.	Last Baby Over 10 lb.	Total	Last Baby Stillborn
Mothers' diabetic curve	0	2	4	5	11	5
Mothers' pre-diabetic curve ..	1	1	2	4	8	3
Mothers' normal curve	41	43	38	24	146	6
Total ..	42	46	44	33	165	14

combined with a fasting level of over 120 mg. or a peak of over 200 mg.; it is considered pre-diabetic if the two-hour or the two-and-a-half-hour level is high but the curve otherwise normal (see Part II).

The main results are expressed baldly in Table VII. This shows only the bare fact that among our 165 mothers we found 11 unsuspected diabetics; in five cases the last baby weighed over 10 lb. and in five it was stillborn. The individual histories and tolerance curves of the 11 diabetics follow:

Results: Diabetic Mothers

Babies 7–8½ lb. (3.2–3.9 kg.)

Mother 1.—Aged 36, coloured, average size. Present infant 8 lb. (3.6 kg.), macerated foetus. Previous 11 pregnancies: "big babies," weights unknown.

Curve

36th week of pregnancy: 159 (fasting), 270, 367, 336, 251, 240.
Sixth post-partum day: 118 (fasting), 174, 174, 190, 221, 201. Sugar ++.

Mother 2.—Aged 38, coloured, average size. Previous five children, 11 lb. (5 kg.), 10 lb. (4.5 kg.), 13 lb. (5.9 kg.), 8 lb. (3.6 kg.), and 9 lb. (4.1 kg.).

Curve

Sixth post-partum day: 279 (fasting), 323, 340, 340, 232, 296. Sugar ++.

Babies 8½–10 lb. (3.9–4.5 kg.)

Mother 3.—Aged 34, coloured, small. Present baby stillborn. Previous children: 9 lb. (4.1 kg.), 8 lb. (3.6 kg.), 6 lb. (2.7 kg.), and 6½ lb. (2.9 kg.).

Curve

Sixth post-partum day: 176 (fasting), 260, 284, 301, 284, 268. Sugar +.

Mother 4.—Aged 45, white. Became obese during pregnancy. Only baby, 8½ lb. (3.9 kg.), premature stillborn. Mother and father both diabetic.

Curve

Sixth post-partum day: 120 (fasting), 206, 222, 181, 136. No sugar.
Six months later: 110 (fasting), 119, 141, 145, 145.
Year later: 106 (fasting), 188, 184, 180, 177, 141. Sugar +.

Mother 5.—Aged 36, coloured, small. Toxaemia in last two pregnancies. Lactation excessive. Nine previous babies of normal weight.

Curve

114 (fasting), 178, 230, 232, 149, 140. No sugar.

Mother 6.—Aged 33, negress, normal size. Eight previous pregnancies produced three stillbirths and four neonatal deaths, with weights of 10 lb. (4.5 kg.), 11 lb. (5 kg.), 12 lb. (5.4 kg.), and 14½ lb. (6.6 kg.) known.

Curve

150 (fasting), 227, 282, 202, 189. No sugar.

Babies over 10 lb. (4.5 kg.)

Mother 7.—Aged 33, coloured, small. Toxaemia with last two pregnancies. Ten previous pregnancies, one stillbirth, none above 9 lb. (4.1 kg.).

Curve

Sixth post-partum day: 130, 226, 243, 230, 178, 144. Sugar +.
Seven months later: 169, 223, 273, 269, 187, 169. Sugar +. Complaining of itching.

Mother 8.—Aged 43, white, obese since childhood. Last child died within 48 hours, weight 15 lb. (6.8 kg.). Previous children, 13 lb. (5.9 kg.) and 16 lb. (7.3 kg.) (neonatal deaths) and twins (live).

Curve

Sixth post-partum day: 247, 299, 346, 337, 287, 255. Sugar ++.

Mother 9.—Aged 46, coloured, slightly overweight. Toxaemia with last pregnancy, and baby weighed 11½ lb. (5.2 kg.), stillborn. Eight previous children, with stillbirth in 1930, none over 9 lb. (4.1 kg.).

Curve

Sixth post-partum day: 118 (fasting), 255 (1 hour), 152 (2½ hours). Sugar +.
Six months later: 229 (fasting), 239, 220 (1 hour), 171, 164 (2½ hours).

Mother 10.—Aged 42, coloured, obese. Ten babies 6–7 lb. (2.7–3.2 kg.), one 11 lb. (5 kg.), and present 10 lb. (4.5 kg.).

Curve

Sixth post-partum day: 219, 230, 268, 296, 262. Sugar +++.

Mother 11.—Aged 39, white, large, rather obese. Baby 11 lb. (5 kg.) stillborn. Aunt is a diabetic. Nine previous babies: last three 12 lb. (5.4 kg.), 10½ lb. (4.8 kg.), and 9½ lb. (4.3 kg.) stillborn.

Curve

171, 207, 199, 199, 171. No sugar.

Several things emerge from an inspection of these protocols. First, 10 out of the 11 women with a diabetic curve had one or more 10-lb. (4.5-kg.) babies and/or one or more stillbirths. Mother 5, with her 9-lb. (4.1-kg.) baby, had had toxaemia in her last two pregnancies and lactated excessively. In *every* case, therefore, there were "diabetic" hints in the obstetrical story. (The high incidence of toxaemia in the diabetic is well attested by Barns and Morgans,[8] White,[29] Mengert and Laughlin,[3] and Patterson and Burnstein.[4])

Secondly, there were no symptoms of diabetes in any parturient case, but Mother 7 complained of generalized itching seven months later.

Thirdly, the average age of the 11 was 37.9 years, as against 25.9 years for the 146 non-diabetic mothers. This striking difference compares with the finding of Gilbert[11] and suggests that several of the younger mothers of large babies may become diabetic later. Incidentally, the average age of all mothers of 10-lb. (4.5-kg.) babies, excluding diabetics, was 31.4 years, which suggests, further, that older women may be more likely to have larger babies. (This is at variance with White and Klein,[17] and is not claimed to be significant.)

Fourthly, maternal obesity was not a very outstanding feature in this series, only 4 of the 11 diabetic mothers being obese, despite their high mean age. This is very different from Gilbert's series in which "all six patients with diabetic blood-sugar curves were 30 lb. (13.6 kg.) or more above their 'correct' weight." It is noteworthy, however, that all three white women in our diabetic group were obese.

Fifthly, *glycosuria* during the tolerance test was absent or very slight in 4 of these 11 mothers, although one was recorded as having shown some sugar during pregnancy. It is plain that these four must have had a raised renal threshold, and it further follows that *an absence of glycosuria does not rule out lowered sugar tolerance in puerperal women.* The renal threshold, therefore, is certainly not always lowered in pregnancy—sometimes the reverse.

Incidentally, no woman in this series showed clinical evidence of hypophysial overactivity, such as the development of markedly acromegaloid features.

Results: Pre-diabetic Mothers

Mother 12.—Negress, aged 20. Only baby premature (said to be 7 months), 4 lb. (1.8 kg.).

Curve

94 (fasting), 140, 189, 165, 156, 105.

Mother 13.—Negress, aged 33, normal size. Present child, 8 lb. (3.6 kg.), living. Glycosuria in pregnancy. Previous baby stillborn.

Curve

(1) 38 weeks antenatal: 90, 124, 153, 136, 153, 90.
(2) 16 days post-natal: 85, 118, 121, 156, 149, 75.
(3) 10 months later: 89, 109, 175, 167, 143, 104.

Mother 14.—Coloured, aged 28, medium size. Present child, 9 lb. (4.1 kg.). Two previous children, 10 lb. (4.5 kg.) and 9½ lb. (4.3 kg.).

Curve
Sixth post-partum day: 94, 138, 149, 151, 133, 91.
Six months later: 95, 150, 130, 130, 130, **130**.
(Repeated-two-and-a-half hour figure alone: **152**.)

Mother 15.—Coloured, aged 29, not obese. All three children 8½–9 lb. (3.9–4.1 kg.). Lactated excessively.

Curve
Antenatal: 82, 114, 139, 143, 143, **142**.
Sixth day: 82, 150, 128, 175, **153**, 121.

Mother 16.—Coloured, aged 30, obese. Only infant 10½ lb. (4.8 kg.).

Curve
81, 126, 155, 184, **177**. No sugar.

Mother 17.—Negress, aged 38. Present baby, 10¼ lb. (4.6 kg.), stillborn. Seven previous children—the four latest over 11 lb. (5 kg.), last one 11½ lb. (5.2 kg.), stillborn.

Curve
93, 133, 188, 180, 156, **140**. No sugar.

Mother 18.—Coloured, aged 43, obese. Present infant 12½ lb. (5.7 kg.), stillborn. Thirteen children, weights unknown.

Curve
99, 128, 133, 156, **152**, 117.

Finally, there was one mother whose curve on the sixth day was "pre-diabetic" in character, but normal on repetition six months later.

Mother 19.—Negress, aged 34, obese. Present child, 10 lb. 2 oz. (4.6 kg.), stillborn. Previous infant, 9 lb. (4.1 kg.), stillborn.

Curve
103, 185, 170, 145, 145, **143**.
Six months later: 82, 153, 114, 105, 85.

Individually, these curves are not very convincing, but all are slightly abnormal in the same way, with high two- or two-and-a-half-hour figures. Then, again, it is highly suggestive that four should be those of women whose recent babies weighed over 10 lb. (4.5 kg.), while of the entire eight there was only one (Mother 12) who had neither large babies nor stillbirths in her history. Furthermore, three of the last babies of these eight mothers were stillborn, compared with six of the babies born to the 146 mothers whose curves were quite normal.

I suggest that this slight aberration in sugar tolerance may be the first indication of the dawning of diabetes, and that these people may later, perhaps only decades later, develop, first, diabetic curves and then overt diabetes. That such "pre-diabetic" curves may really be of significance is shown by John,[28] who was able to demonstrate the transition into true diabetes in several cases, and who makes the challenging statement, "Even the slightest elevation of blood sugar cannot be ignored, since it is likely in later years to progress into frank diabetes." Lambie[26] in 1926 and Skipper[14] in 1933 suggested that a diminished carbohydrate tolerance during pregnancy might progress to true diabetes in later years. Skipper showed further that "diabetes" during pregnancy does not really disappear after childbirth, even though the curve may become normal (Wiener[31]; Strouse and Daly[29]), for the diabetic state always reappears later. Consequently one would feel that Mother 4 is still, at least potentially, diabetic, despite the improvement in her sugar tolerance, and that this probably applies also to Mother 19, especially as her two babies were both large and stillborn.

The Meaning of "Diabetic"

It is evident from the foregoing and from the work of John[28] and the experience of many physicians that some people must be walking about for years blissfully ignorant of their lowered sugar tolerance. If this state is discovered, as in this investigation, I suggest that it should be called "chemical diabetes" in contradistinction to that overt or clinical diabetes which is manifested by characteristic symptoms. This chemical diabetes—and perhaps even the "pre-diabetes" in which only the two or two-and-a-half-hour tolerance figure is raised—may nevertheless make itself felt in the production of large babies, babies who are macerated or stillborn or who die soon after birth, maternal obesity, and, possibly, an increased liability to toxaemia of pregnancy and over-lactation. It follows, further, that many of our "new" female diabetic patients have really been chemically diabetic and pre-diabetic for many years, and that their previously unsuspected metabolic abnormality is correlated with an abnormal obstetrical history.

Importance of the Discovery of Chemical Diabetes

Lower carbohydrate tolerance could often be discovered by performance of tolerance curves on all women who had repeated large babies and/or stillbirths; but would this be of any value? I suggest it might be, in two ways: (1) a moderate carbohydrate (120–200 g.) and low-calorie diet might prevent the emergence of overt diabetes and even rectify the biochemical abnormality, especially if the patient is obese[25]; and (2) a living child might be obtained from a further pregnancy if the methods of White[21 30] were adopted to correct any hormone imbalance in later pregnancy (though her conclusions have not everywhere been confirmed). Certainly these chemical diabetics seem to have a foetal death rate (5 out of 11) as high as that of any full diabetic series.

The importance of the pre-diabetic curve is more doubtful, though a person possessing one, with a suggestive obstetrical history, should at least be carefully watched in the future, especially since the stillbirth rate in this series was three out of eight, as against six out of 146 in the normal group.

Maternal Obesity and Large Babies

It has already been seen that the present series does not show any remarkable association between maternal obesity and abnormal sugar tolerance. There seemed to be some relationship, however, between maternal obesity and large babies; thus there was only 1 obese mother out of 41 with babies under 7 lb. (3.2 kg.); 4 obese out of 43 with babies 7–8½ lb. (3.2–3.9 kg.); 5 obese out of 38 with babies 8½–10 lb. (3.9–4.5 kg.), and 9 obese out of 25 with babies over 10 lb. (4.5 kg.). These proportions are expressed graphically in Fig. 4, and are statistically significant ($\chi^2 = 18$, d.f. = 3, $P < 0.01$). This finding agrees with Odell and Mengert,[27] Gilbert,[11] and Sheldon,[13] although Klein[17] believes that there is no correlation between maternal and foetal size, and reviews the conflicting literature on the subject.

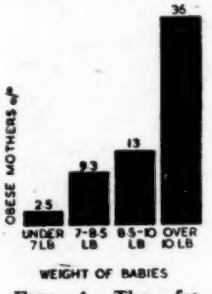

FIG. 4.—The frequency of obesity in mothers compared with the birth weights of their babies. There appears to be a positive correlation between maternal obesity and birth weight.

Summary

The existence of the maternal pre-diabetic state, during which there is a tendency to produce large babies or stillbirths, is shown to exist in the various races in the Cape. It is, moreover, found that this tendency is present for an indefinitely long period before manifest diabetes develops, even over 30 years.

Consideration of the children of diabetic *fathers* also indicates that their birth weights are above normal, while the stillbirth rate is not altered. It is realized that these results, though significant statistically, need corroboration from larger centres. They suggest that the onus of the production of large babies cannot be entirely borne by maternal hormones, but must in part be an inherited phenomenon, linked in some way to the diabetic genetic constitution of *either* parent.

An attempt has been made to discover early diabetics and those who are probably in the pre-diabetic phase by performing glucose-tolerance tests on mothers who were delivered in hospital of babies weighing over 10 lb. (4.5 kg.). In Part II we show that examination on the sixth post-partum day gives valid results. Mothers whose babies fell into lower weight groups were also tested for comparison.

Eleven unsuspected diabetics were disclosed out of 165 mothers. Of these, 10 had had babies over 10 lb. (4.5 kg.) and/or one or more stillbirths, while the eleventh had had toxaemia in her last two pregnancies. Their average age was high, only four were obese, and in four cases there was no glycosuria during the tolerance test.

A further eight mothers gave curves with high two-hour or two-and-a-half-hour levels, and are considered to be probably "pre-diabetic." It was very interesting to note that *all but one* had had large babies and/or stillbirths.

It is suggested that many "new" female diabetic patients have really been chemically diabetic or pre-diabetic for several years, and that this previously unsuspected minor metabolic abnormality is correlated with an abnormal obstetrical history. Consequently, examination by tolerance curve of all women who give birth to babies over 10 lb. (4.5 kg.) in weight or to unexplained stillbirths should reveal many potential diabetics. With this knowledge it might then be possible to prevent the development of overt diabetes or of further foetal loss.

Finally, our figures suggest a positive correlation between maternal obesity and infant birth weight.

Addendum to Part I

Bringing our figures up to date, we have now discovered 16 entirely unsuspected diabetic mothers by testing on the sixth post-partum day. Their last babies in nine cases weighed over 10 lb. (4.5 kg.) and eight were stillborn. Eleven other mothers gave a pre-diabetic curve, six of whose last babies were over 10 lb. (4.5 kg.) and five were stillborn.

In our obstetric department "pre-diabetes" has become a *clinical* diagnosis based on the previous obstetric history.

PART II

SUGAR TOLERANCE IN LATE PREGNANCY AND EARLY PUERPERIUM

It is common knowledge that the carbohydrate metabolism is altered during pregnancy. A lowered glucose tolerance was even mooted as a pregnancy test.[32 33] However, a search in the literature for authoritative information on glucose tolerance near term and in the puerperium was surprisingly unrevealing. Moss and Mulholland[7] cite seven references to tolerance curves during normal pregnancy. Four of these do not even mention such curves; one[34] states that tolerance is abnormal in 8% of pregnancies, but gives no further information; one[35] simply reports that no difference in the intravenous test was found between pregnant and non-pregnant women. Williams and Wills,[36] after 100 g. of glucose, found high two-hour to three-hour figures in a large proportion of pregnant and parturient women, the curve within ten days of delivery being invariably abnormal. Hurwitz and Jensen[37] used Folin's method on capillary blood, giving 1 g. of glucose per kg., and report in 25 healthy pregnant women fasting levels below 120 mg., and peaks below 200 mg., but very frequent two-hour values above 120 mg., especially in late pregnancy and the puerperium.

It was necessary for our investigations (see Part I) to know what sort of tolerance curves are usually obtained in the early puerperium by our methods. As the literature was insufficient for this purpose we have made our own observations, both in late pregnancy (36th week) and soon after childbirth (sixth day).

"Normal" Glucose Tolerance

Before proceeding it is necessary to define the range of normality of the tolerance curve. Unfortunately, authorities greatly differ in method of administration of glucose, in type of blood sample, in method of sugar estimation, and in interpretation. A consideration of the various points of view is beyond the scope of this article, and the reader is referred to discussions specifically concerned with this subject.[38–44] There emerges fairly general agreement:

(1) That the subject's recent diet must be unrestricted in regard to carbohydrates.

(2) That the "standard" one-dose (50 g.) glucose test is probably the best.

(3) That fasting and half-hourly readings up to two hours, and preferably two and a half or three hours, are necessary for full evaluation.

(4) That capillary blood gives the same fasting reading as venous, but is variably higher (up to 50 mg.) postprandially. It is impossible to say which gives "better" readings, but capillary blood is easier to obtain and does not miss the "lag" type of curve.

(5) That the Folin and the Hagedorn–Jensen types of sugar estimation give readings 10–20 mg. higher than the "true" blood sugar.

(6) That the fasting level is important, anything over 120 mg. (Hagedorn–Jensen) being highly suggestive of diabetes. On the other hand, a *lower level does not exclude reduced tolerance.*

(7) That the maximum reading is of little importance, although it should seldom exceed 200 mg. (capillary blood).

(8) That the two-hour level is of the greatest significance, figures above 140 mg. (capillary blood, Hagedorn–Jensen) definitely indicating lowered tolerance, while between 120 and 140 mg. is the doubtful range. Two-and-a-half to three-hour levels may be helpful where the two-hour reading is doubtful, and should certainly be not above 130 and 120 mg. respectively.

It is plain that there are all gradations of glucose tolerance, which does not even remain fixed from time to time in the same person, so that one cannot draw a sharp line to separate diabetes from normal. Our "normal" curve, therefore, lies below: fasting, 120 mg.; highest level, 200 mg.; two-hour level, ? 120 mg., certainly under 140 mg. (capillary blood, Hagedorn–Jensen).

Methods.—For this study we have taken at random 42 women attending the antenatal clinic at Groote Schuur Hospital and performed tolerance tests at the 36th week, and 140 mothers on their sixth post-partum day. Twenty-seven women were tested at both times. We have excluded known diabetics, all curves which were found to be diabetic or "pre-diabetic" (see Part I), and curves after caesarean section. All the women were either coloured (half-caste) or native (negresses). Their diet is on the whole high in carbohydrate, and childbirth only very briefly interfered with their intake.

We have used the 50-g. standard test, capillary blood, the Hagedorn–Jensen[44] estimation, and criteria of normality given above.

Results

Fasting Level.—On the whole the fasting levels were lower both at the 36th week and post partum than are found in general. The mean late pregnancy level was 83 mg., and the puerperal level 90 mg. (cf. Hurwitz and Jensen[37]). *No single fasting level was above 120 mg.* unless the curve was otherwise abnormal and definitely indicated lowered tolerance. On the other hand, four curves which were otherwise frankly diabetic had fasting levels below 120 mg.

Maximum Level.—Antenatally this averaged 128 mg. at one hour and 137 mg. post-natally. The significance of a high level, above 200 mg., was very similar to a high fasting sugar. *Not one curve which was otherwise normal showed a figure above 200 mg.* (excluding post-caesarean cases and two plainly technical errors). The only "lag" curve

discovered was after a caesarean section. Not all diabetic curves exceeded this level, nor did any of the "pre-diabetic" group (see below).

Two-hour Level.—Two out of 42 antenatal and 20 out of 140 post-natal curves exceeded 120 mg. at two hours; all were below 130 mg. at two and a half hours. Such curves are regarded as probably normal, although if accompanied by a suggestive obstetrical history (stillbirths and large babies) they should be repeated later. Figures *above 140 mg. at two hours* and 130 mg. at two and a half hours are very highly suspicious, and were found in eight cases (see Part I). *In all but one of these there was an obstetrical history suggestive of "pre-diabetes."*

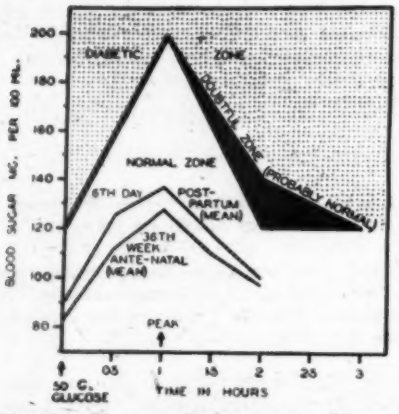

FIG. 5.—Glucose-tolerance curves. Upper thick curve shows the maximum normal. Lower curves are means of patients examined after sixth day post partum and at 36 weeks antenatal.

Curve as a Whole.—The mean post-natal curve runs at a higher level than that obtained from 36th-week examinations (Fig. 5). This tendency is confirmed by consideration of the 27 women tested at both times, 14 of whose post-natal curves were higher and only six lower, seven being virtually unchanged. Williams and Wills[36] also found a comparatively higher curve after delivery.

Conclusions Regarding Tolerance at 36th Week and Sixth Day Post Partum

It is plain that these figures, based on larger numbers of cases than elsewhere in the literature, do *not* confirm the usual contention that glucose tolerance is lowered in *normal* pregnancy and puerperium, at least not near to the time of delivery. At the very outside estimate, and applying the most stringent criteria (120 mg. fasting, 200 mg. peak, 120 mg. at two hours), only 30 curves out of 182 have a single figure outside normal, and we have reason to believe that several of these are truly "pre-diabetic."

This is very different from Williams and Wills's[36] finding of frequent markedly lowered post-partum tolerance, and Hurwitz and Jensen's[37] series in which half showed two-hour levels of over 120 mg. We conclude that *any lowering of carbohydrate tolerance in late pregnancy or the puerperium is probably abnormal.*

Melituria during the tolerance test was noted in about 20% of cases only. This is less than usually reported, but we regarded a result as positive only if a definite orange precipitate was formed with Benedict's reagent. It had no relation to the birth weight of the baby or to foetal loss. In some cases glucose was present with a low renal threshold, while in others the reducing substance was lactose. *Obesity* in this series had no relation to the tolerance curve.

Caesarean Section

Ten tests were made six days after caesarean section had been performed on the mothers. Five of these showed much reduced tolerance, but had all returned to normal when retested some months later. Operation itself is known to alter carbohydrate metabolism, and it is concluded that an abnormal tolerance curve is of no significance shortly after a caesarean section.

Conclusion and Summary

Using the 50-g. single-dose capillary blood and the Hagedorn–Jensen method for blood sugar, we have defined a normal glucose-tolerance curve at the 36th week and on the sixth post-partum day as below 120 mg. fasting, with a maximum level below 200 mg., a two-hour level below 140 mg., and a two-and-a-half-hour level below 130 mg.

Two-hour levels between 120 and 140 mg. are slightly suspicious but probably normal.

Two-hour and two-and-a-half-hour levels above these limits, with the rest of the curve normal, are often regarded as expected findings in pregnancy, but we believe they are a warning of "pre-diabetes" (cf. Lambie,[26] Skipper,[14] and John[25]).

Two-hour levels over 140 mg. with a high fasting level and a high maximum level, or diabetic symptoms, must be regarded as frankly diabetic.

Patients suspected of being diabetic may be expected to yield reliable information by testing on the sixth day after delivery.

I am grateful to Professor F. Forman and Professor G. C. Linder for their encouragement and helpful criticism. It is a pleasure to acknowledge the excellent technical assistance given by Miss E. Scholtz and Mrs. M. A. van Heerden. Part of the cost of this investigation was defrayed by a grant from the Staff Research Fund of the University of Capetown.

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Home-grown prunes will soon be on the market. There was a glut of plums this year in many parts of England, and growers faced serious losses. To meet the situation the Agricultural Co-operative Association, with the support of the Ministry of Food, sponsored a scheme to convert the surplus plums to prunes. Some 170,000 lb. (77,000 kg.) of plums were dried, yielding 30,000 lb. (13,600 kg.) of prunes.

PAINFUL SPASM OF THE OESOPHAGUS ("CORKSCREW" OESOPHAGUS)

BY

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In 1933 Schatzki suggested the term "kräuselung," or *curling*, for an uncommon condition of the oesophagus which seems to be little known outside the field of radiology (Scheinmel *et al.*, 1949). In this condition alternating contractions and dilatations of the oesophagus occur as a result of multiple segmental spasms affecting it below the level of the aortic arch. Teschendorf (1928) aptly described the lower end of the oesophagus as resembling a string of pearls. This condition, however, is better known as "corkscrew" oesophagus.

The spasms do not always encircle the oesophagus, but may occur anteriorly, laterally, and sometimes posteriorly (Palugyay, 1931). During radiographic examination spasms occur spontaneously, but they can also be brought out by distending the oesophagus with barium; they become more pronounced when the patient lies flat. Spasms may be persistent or evanescent. The oesophagus may be partially or completely occluded by these spasms, and stasis occurs.

This condition usually arises after middle age, but has been reported in the second and third decades (Templeton, 1944). The contractions are usually more prominent in older patients, and males are affected more often than females.

Symptoms

There may be no symptoms, and Scheinmel *et al.* (1949) have suggested that more cases would be found by diligent and routine radiological studies of the oesophagus. The following symptoms have been described: severe or moderate pain in the chest occurring during swallowing or whenever the spasms are present, progressive dysphagia, which may become complete (Reich, 1929), and postprandial regurgitation. When pain occurs its severity may parallel the degree of spasm (Scheinmel *et al.*, 1949). Symptoms may be present for many years.

The pathological physiology of this condition is not known. It has been variously attributed to reflex spasm of the oesophagus, "fibrous scarifying mediastinitis," and para-oesophageal adhesions; and to have been associated with duodenal ulcer, traction, oesophageal diverticula, achalasia of the cardia, and carcinoma of the oesophagus.

An imbalance of the neuromuscular mechanism has been put forward by Carlson (1922) and Teschendorf (1928). This seems to be the most likely explanation.

Penner and Druckerman (1942) described "corkscrew" oesophagus in two patients with Parkinsonism and thought there might be some association between the two conditions. They felt that, as the extrapyramidal system is concerned in the co-ordination of successive movements, deglutition would be significantly affected in Parkinsonism. Jacob (1923) also states that the entire act of deglutition is affected in extrapyramidal disease. Templeton examined the oesophagus in six cases of Parkinsonism, and saw multiple spasms in only one case. He felt that the conditions were not related. Scheinmel *et al.* (1949) dogmatically stated that the finding of Parkinsonism is coincidental.

Necropsies have been carried out; Reich (1929) found nothing abnormal. Templeton examined the oesophagus in five cases but found only slight mucosal thickening and fibrosis. No note is made of any change in the autonomic ganglia of Auerbach's plexus; in fact, no definite changes were found in the muscle walls at all.

Changes in the mucosa have been described in the living patient. Johnstone (1946) described the case of a man aged 66 who had had two attacks of complete but transient dysphagia in 12 months. Examination of this patient's oesophagus with an oesophagoscope showed loose folds in the mucous membrane. McLaren (1946) described the case of a woman aged 60 who had similar symptoms and was found on oesophagoscopy to have a narrowing of the oesophagus below the aortic arch.

Treatment

Scheinmel *et al.* (1949) tried various drugs in the treatment of this condition: (*a*) atropine sulphate, 1/100 gr. (0.65 mg.) by injection every four hours for two to four doses; (*b*) tincture of belladonna, 15 min. (0.9 ml.) three times a day for 4 to 14 days; (*c*) amphetamine sulphate, 5 mg. orally every 4 hours for 36 hours; and (*d*) inhalations of amyl nitrite.

They found that atropine and belladonna may reduce the degree of spasm and relieve the symptoms in some cases and abolish them in others; amyl nitrite was very effective, but its action was short. Amphetamine produced more prolonged relief than any of the other drugs. However, Schinz *et al.* (1932) found that the condition was rarely influenced by atropine.

Case Report

A shoemaker aged 70 came to the out-patient department in September, 1951, stating that he had suffered from attacks of pain in the centre and right side of the chest for three months. This pain was severe and burning, and made him cry out. Attacks were precipitated by eating, drinking hot fluids, lying back in a chair, and stooping forwards. His symptoms were worse at night-time, when he lay back in bed; he had, in fact, learnt to sleep propped up. Relief could sometimes be obtained by drinking cold water.

His symptoms were not affected by exertion. There was no dysphagia. His appetite had not deteriorated, but he was unable to enjoy his meals because of the pain produced by swallowing. In addition he had intermittent claudication in the left leg, dyspnoea, and severe headaches, and had recently had a brisk epistaxis. As a young man he had had an empyema on the right side of his chest. This had been drained surgically, and ever since he had had a cough and brought up a slight amount of purulent sputum. His family history was negative.

When examined he was found to be very emotional, and was having very severe attacks of pain. These attacks were precipitated by making him lie flat. General physical examination revealed tortuous radial arteries, arterial hypertension (260/140 mm. Hg), and enlargement of the left ventricle. There was slight clubbing of the fingers; the chest was emphysematous, and the empyema drainage scar was visible. In addition, coarse crepitations were audible at the bases of both lungs. The abdomen and the central nervous system were normal.

An *x*-ray film of the chest showed pleural thickening on the right side and changes suggestive of bronchiectasis at the base of the right lung. The aorta was prominent, but there was no evidence of calcification in it. When the patient swallowed barium the oesophagus below the level of the aortic arch was seen to be repeatedly broken up by violent circular contractions—the "corkscrew" effect (Figs. 1 and 2). These contractions appeared very frequently and became more obvious when the patient lay flat. They were associated with the severe pains in the chest. Between the attacks of spasm the oesophagus appeared normal. There was no evidence of obstruction or "hiatus" hernia.

For 34 days he was treated with atropine sulphate, 1 mg. three times a day by mouth. This brought obvious symptomatic relief, and he was then having symptoms only when he lay back. Screening showed that the spasms were less prominent and less frequent. Atropine was withheld and the symptoms returned in full force; the contractions were seen to become more frequent.

FIG. 1. — Postero-anterior view, showing corkscrew effect.

FIG. 2.—Right lateral view, showing beginning of spasm.

Amyl nitrite did not reduce the frequency of the contractions, and did not relieve the symptoms. He was given 0.75 g. of pentamethonium bromide ("lytensium" syrup) by mouth. Within five minutes relief from his symptoms occurred which lasted for 30 minutes and was more complete than with atropine. Unfortunately, he refused to have further radiographic examinations, and so it was not possible to note the effect of pentamethonium bromide on the oesophageal contractions. He also refused to have an oesophagoscopy carried out and he left hospital. Further treatment with atropine was advised.

Discussion

There is no doubt that this is a very uncommon condition. It seems that it is most likely to be due to a neuromuscular incoordination secondary to degeneration of the autonomic plexuses in the wall of the lower oesophagus. What actually produces this degeneration is not obvious, but it may be impairment of the blood supply to the oesophagus due to arteriosclerosis; an analogous condition is "mesenteric angina." In necropsies carried out on elderly subjects with arteriosclerosis Mosher (1933) noted sclerotic changes in the arterial supply of the oesophagus and changes in the wall of the oesophagus; he thought that the two were associated. The latter, which also included the nerve plexuses, varied from lymphocytic infiltrations to fibrosis. These changes began in the lower part of the oesophagus. If this condition is due to arteriosclerosis then that would account for its tendency to occur in elderly people.

The exact innervation of the oesophagus in man is not known (Templeton, 1944). The main motor supply seems to come from the vagi (Templeton, 1944; Alvarez, 1949). Observations in animals have shown that stimulation of the vagi produces tetanic contractions of the whole of the oesophagus (Kahn, 1906; Inaoka, 1924; Knight, 1934–5). The former workers stimulated the smaller branches of the vagi before these entered the oesophagus and produced localized segmental spasm. The vagi were shown to terminate in the mesenteric plexuses.

The part played by the sympathetic nerve supply is debated. Jurica (1926), working with cats, found that it had little effect on the function of the oesophagus. Ottaviani (1937), however, thought that the main nerve supply to the oesophagus was from the sympathetic nervous system. Knight found in animals that the tetanic contractions produced by stimulation of the vagi were augmented in the upper oesophagus and inhibited in the lower by stimulation of the sympathetics. Bilateral section of the vagi produced achalasia, but this did not occur if the sympathetic nerve supply was removed beforehand. On the whole it would seem that the sympathetic nerve supply is inhibitory.

Atropine presumably relieves the spasms by inhibiting the vagi and by its action on smooth muscle. Pentamethonium bromide probably acts by exerting a ganglion-blocking effect, and the question arises whether it produces this effect locally. Amyl nitrite, when it produces relief, must do so by causing the relaxation of smooth muscle; this was not seen to occur in the case described above.

Summary

The condition "corkscrew" oesophagus is described, and the literature reviewed.

It is suggested that this condition is due to degenerative changes taking place in Auerbach's plexus as a result of arteriosclerosis.

A case is reported, and the effects of treatment are noted.

I am grateful to Dr. H. A. Dewar for permission to report this case. I thank Dr. I. B. D. Middlemass for the radiographic reports and Dr. Whateley Davidson for permission to reproduce the radiographs. I have also to thank Mr. C. J. Duncan, of the department of photography, King's College, for permission to reproduce the radiographs.

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A CASE OF IDIOPATHIC PORPHYRIA

BY

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In 1937 Harrison drew attention to the presence of two porphyrins—uroporphyrin and coproporphyrin (stercoporphyrin)—in cases previously described as haematoporphyrinuria, and that porphyrinuria may occur in three main conditions: (1) susceptibility to drugs such as sulphonal, methylsulphonal, barbitone, etc.; (2) inborn errors of metabolism—that is, "congenital porphyrinuria"; and (3) acute porphyrinuria not due to drugs. In these there may be deposits of pigment in bones and teeth.

Very little has been added to the literature in regard to new clinical features, aetiology, classification, and treatment, but it is hoped that the case presented might prove of interest. Brief reference is made to available literature.

Case Report

The patient was a man aged 27. In December, 1944, while still an air gunner with the R.A.F., he complained of stabbing pain in the left hypochondrium. Later this

passed to the right hypochondrium, and he noticed that his urine was dark red. No pain or frequency was associated with the act of micturition. Nausea was present and he perspired profusely. No pain occurred elsewhere; there was no headache or giddiness, and no loss of weight at this time.

He was admitted to an R.A.F. hospital; his appetite had become poor, his bowels were constipated, and he experienced difficulty in starting the act of micturition. The condition was apparently variable under symptomatic treatment, but one month later he developed pains in the legs. These were sharp and shooting in character, and he also had a sensation of "pins and needles" in the feet. Movement greatly aggravated the pains. He was discharged from hospital nine months later, and the pain, though still present, was less severe and less frequent. Six months afterwards he stated that his arms and hands suddenly became "paralysed" and were painful. This condition existed for approximately two weeks and then disappeared rapidly. It seems that there was no complete paralysis and that gross movements were at all times retained. He said he was told that his face became blue during attacks; but the question of true cyanosis seems to be in doubt. Some mental confusion occurred during severe attacks.

He was first admitted to Ayr County Hospital on September 21, 1945, and from then until February 9, 1948, he had 11 attacks, requiring admission to hospital here. Treatment was for the most part symptomatic. On other occasions he was admitted to the Western Infirmary, Glasgow. His last attack was early in October, 1950, and the last severe one in September, 1950. There had been no other illnesses of note. The patient works as a labourer.

Family History.—His father is alive and well; his mother died of cerebral haemorrhage at 56. Three brothers and two half-brothers are all healthy. There is no Scandinavian link in his family.

The patient was admitted to Heathfield Hospital on November 6, 1950, for review, though he had no complaint at that time. Clinical examination revealed a fit, healthy-looking individual. His weight appeared to be static at 9 st. 7 lb. (60.3 kg.). While in the R.A.F. his weight was 12 st. (76.2 kg.), and his lowest during the early attacks was 7 st. 7 lb. (47.6 kg.). There was slight clubbing of the fingers of both hands. Apart from slightly diminished left biceps- and triceps-jerks no abnormality was detected in the central nervous system. Muscle power was good and there was no wasting. His blood pressure was 118/80, and no clinical abnormality was elicited in the other systems.

Examination of the blood showed: urea, 62 mg. per 100 ml.; red cells, 4,130,000; Hb, 82% (11.48 g.%); white cells, 5,200 (neutrophils 60%, lymphocytes 33%, eosinophils 2%, monocytes 5%); P.C.V., 38%; M.C.V., 92.7 μ^3; M.C.H.C., 30.2%. The red cells were normocytic and normochromic. An intravenous pyelogram showed no abnormality. An attempt was made to demonstrate fluorescence of sternal marrow under ultra-violet rays, but this was unsuccessful. Plasma chloride amounted to 550 mg. NaCl per 100 ml. Total porphyrin in the urine was 1.5 mg. per litre; uroporphyrin, 960 µg. per litre; coproporphyrin, 40 µg. per litre. The urine contained some urobilinogen, but no bilirubin could be detected. The porphyrin so far isolated has been an isomer of Series III.

Investigation in April, 1947, showed a somewhat similar picture. The blood urea on this occasion was 48 mg. per 100 ml., and again the plasma chloride was low. The diastase index was normal to high. All other investigations proved negative, and at no time has there been hydroa aestivale. Treatment included the administration of morphine, spinal analgesia, sodium chloride, "eucortone," and vitamin B.

Over the past two years acute attacks have become less frequent and less severe, though he still continues to excrete excessive amounts of urinary porphyrins.

Comment

In recording cases certain authors (Watson, 1937, 1947; Berg, 1945; Petrie, 1948; Davies, 1949, and others) have drawn attention to features which might be predominantly abdominal, nervous, or mental, and in the light of present knowledge Gray, Rimington, and Thomson (1948) suggest Waldenström's classification as probably the most acceptable:

(1) *Porphyria Congenita.*—Familial, and probably recessive in character, present at birth; there is sensitivity to light and pigmentation of bones and teeth; coproporphyrin and uroporphyrin present mainly as Series I.

(2) *Porphyria Cutanea Tarda.*—Here porphyrinuria and sensitivity to light develop later in life and a sclerodermic tendency is noted. There is colic and the occasional excretion of large quantities of uroporphyrin (Series III). Severe nervous symptoms are not present.

(3) *Porphyria Acuta.*—Familial, and accompanied by the excretion of coproporphyrin and uroporphyrin, mainly of Series III. The following clinical forms have been recognized: (*a*) *latent:* increased uroporphyrin excretion without any clinical manifestations of porphyria; usually there are relatives with overt forms; (*b*) purely abdominal form; (*c*) purely nervous form; (*d*) classical acute, with abdominal colic and paralysis; and (*e*) comatose form—that is, where coma predominates in the terminal phase.

Gray *et al.* record a case of porphyria cutanea tarda. In contrast Kiloh and Nevin (1950) report a case which might well belong to category 3(*d*).

In a personal communication Professor C. J. Watson, of Minnesota, where there is a predominance of Scandinavian stock, indicates that porphyria is unlikely to be more common in them, and he is ready to think it is simply a question of recognizing the condition.

Summary

A case of idiopathic porphyria is presented and certain literature reviewed. No congenital feature has been depicted. In the earlier episodes all attacks were acute. More recently, attacks have been less frequent and less severe, and, since the patient excretes porphyrins between attacks, the condition might now be stated to be chronic. However, if we are to accept Waldenström's classification this case would appear to fit the third category as outlined above. Nervous manifestations have been minimal, and as he is beyond the five-year period, during which mortality is put forward as 80%, his position in the subsections of this third category is still in doubt.

Although this case showed a rather high blood urea and a somewhat low plasma chloride it is felt that much more material is required before correct evaluation of blood chemistry figures can be made.

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Over eight million tons of household refuse are disposed of each year in England and Wales at a cost of over £5m. These figures were given by Professor R. H. Stoughton at the recent International Horticultural Congress in London (*The Times*, September 10), when he was discussing measures to combat impoverishment of the soil. If to this were added the vast quantities of sewage sludge which are dumped in the sea or otherwise denied the land—the northern outfall works of the L.C.C. alone accounts for two million tons a year—the loss was indeed formidable. Professor Stoughton then described efforts to make compost from these two waste materials; preliminary results were encouraging.

THE AETIOLOGICAL SIGNIFICANCE OF GEOGRAPHICAL VARIATIONS IN CANCER MORTALITY

BY

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In a previous communication (Legon, 1951) it has been suggested that the areas of heaviest total cancer mortality in England and Wales are the areas of soils richest in organic matter, and that these heavy mortalities may be related to the micronutrient deficiencies that sometimes appear in crops grown on peat soils. The purpose of the present paper is to examine this hypothesis in the light of quantitative data on soils and of recently published work on plant copper metabolism.

Regions of Abnormal Total Cancer Mortality in England and Wales

Fig. 1 depicts the counties and groups of counties in which total cancer mortality is almost certainly abnormal. They are the counties that showed consistently high or consistently low mortalities for all cancer in the analyses of Stocks (1928) and Stocks and Karn (1931). It does not follow that the rest of England and Wales has a normal mortality, nor that the counties shown on the map have abnormal mortalities over the whole of their areas. All that can be deduced with certainty is that abnormal total cancer mortalities must prevail among a large proportion of the populations resident in the counties shown here, and that true regions of abnormal total cancer mortality exist in the general areas of these counties, but are almost certainly not coextensive with them.

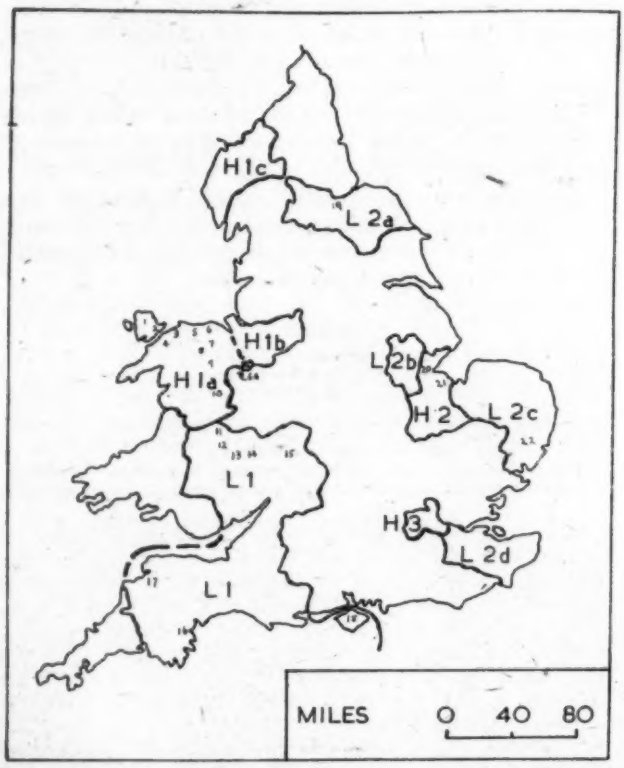

FIG. 1.—The areas of abnormal total cancer mortality in England and Wales (see text). Small figures refer to soil samples (see Table I); these were obtained from the most populous agricultural parts of the areas when possible.

The areas may be described as follows, with details of mortality from cancer of particular sites based on the detailed studies of Stocks (1936, 1937, 1939):

High-mortality Areas.—H1: The high-mortality areas of the north-west. H1a: North Wales, including the counties of Anglesey, Caernarvon, Denbigh, Flint, Merioneth, and Montgomery. The total excess in this area results from a huge excess for gastric cancer and a smaller excess for intestinal cancer. Most other sites show deficiencies. H1b: Cheshire shows a large excess for gastric cancer, but several other sites have excesses. H1c: Cumberland shows markedly excessive mortality from intestinal cancer. H2: The high-mortality area of the Fenlands includes the counties of Ely, Huntingdon, Peterborough, and Lincoln (Holland). In this area all sites show excessive mortalities except the lung, the larynx, and the tongue, mouth, and jaw (as one site). H3: The London area of high mortality consists of the counties of London and Middlesex. Respiratory sites show marked excesses, while the stomach does not.

Low-mortality Areas.—L1: The low-mortality area of the south-west includes the counties of Radnor, Brecon, Hereford, Worcester, Gloucester, Glamorgan, Devon, and Dorset, and the Isle of Wight. Many sites show deficiencies. L2: The low-mortality areas of eastern England include the counties of (*a*) the North Riding, (*b*) Lincoln (Kesteven), (*c*) Norfolk and East Suffolk, and (*d*) Kent. Many sites show deficiencies.

Grouped under these two broad headings are areas of the most diverse physical and cultural landscapes; and this, together with the variations of site distribution, discourages the idea that common conditioning factors may underlie the variations in total cancer mortality. Nevertheless, it seemed that some association might exist between total cancer mortality and the organic content of the soil on which much of the vegetable food supply is grown. Thus the heavy rainfall of North Wales and Cumberland, together with their glaciated topography, is likely to give rise to waterlogging and the accumulation of peat; and the high organic content of the original soil may well have been maintained by the dung of the large flocks of hill sheep kept in these areas. In Cheshire, a fairly heavy rainfall and a subdued relief have led to the formation of "mosses," considerable areas of which are now under cultivation: and large numbers of dairy cattle are kept in proportion to the arable acreage of the county. The four Fenland counties contain relatively large areas of peaty soils which have long been under cultivation, and which produce for the London market.

The low-mortality areas of the east are for the most part well drained, and their agriculture is largely arable, so that excessive dunging of cultivated land is improbable. The areas of peat that occur in Kesteven and Norfolk are small in proportion to the total arable area in either county. The low-mortality area of the south-west has conditions of good soil drainage in its populous cultivated parts, and it is probable that the "hungry" nature of the soil over much of the area may offset manuring from the strongly developed pastoral side of its agriculture.

Ignition-loss Test

Unfortunately, quantitative data on the organic contents of British soils are rare. I therefore obtained soil samples from as many of the areas as possible, and subjected them to an ignition-loss test similar to that described by Marbut (1935). The samples consisted of approximately 5 c.cm. of top soil from at least two arable fields, and were taken by local residents unaware of the ultimate objective of the survey.

The ignition-loss figure (Table I) includes loss of water not removed by the initial drying of the sample and the loss of carbon dioxide from calcium carbonate, in addition to the loss from the combustion of organic matter. Since none of the samples came from a clay area, variations in the

TABLE I.—*Cultivated Soil Ignition-loss in the Areas of Abnormal Total Cancer Mortality*

Area	County	Sample	Ignition-loss % Dry Weight	Remarks
H1a	Anglesey	1, 2	12·2, 10·6	Mixed samples from separate rural districts
	Caernarvon	3, 4	13·2, 12·1	No. 3 very slightly effervescent with HCl
	Denbigh	8, 7, 5	13·6, 12·7, 12·6	Mixed samples from separate rural districts
	Flint	6, 6A	7·3, 4·8	Rural districts of abnormally low gastric cancer mortality
	Merioneth	9	14·3	Mixed sample from one rural district
	Montgomery	10	10·8	
H2	Lincoln (Holland)	20	18·6	Highly effervescent with HCl. Peaty
	" "	21	10·6, 7·3	Non-peaty
L1	Radnor	11, 12	8·6, 8·7	Mixed samples from separate rural districts
	Hereford	13, 14	9·0, 7·1	Some effervescence with HCl
	Worcester	15	11·8, 4·2, 9·5, 7·9	
	Devon	16	11·8, 9·1	Highly effervescent with HCl
	"	17	7·1	
	I. of Wight	18	7·3	Mixed sample
L2a	N. Riding	19	10·2, 7·3, 5·9	
L2c	E. Suffolk	22	6·9	Mixed sample. Some effervescence with HCl

loss of water are probably not serious; and the cases in which loss occurred through the decomposition of calcium carbonate are indicated by the qualitative acid test. It would therefore seem that soils in the high-mortality area of North Wales are indeed rich in organic matter, and that soils of considerably lower organic contents are common in the low-mortality areas of the south-west, the North Riding, and East Suffolk.

Gastric Cancer Mortality and Soil Ignition-loss in North Wales Rural Districts

Fig. 2 shows the standardized gastric cancer mortality ratios (Legon, 1951) of the North Wales rural districts for which soil samples have been obtained. There seems to be a close association of mortality from gastric cancer with the ignition-loss of the soil except in the case of Aled Rural District.

TABLE II.—*Gastric Cancer and Cultivated Soil Ignition-loss in North Wales Rural Districts*

Mortality Ratio	Rural District	Ignition-loss % Dry Weight
Over 175	a. Hiraethog	13·6
	b. Penllyn	14·3
145–175	c. Gwrfai	12·1
	d. Ogwen	13·2
	e. Ruthin	12·7
	f. Twrcelyn	12·2
115–145	g. Aethwy	10·6
	h. Llanfyllin	10·8
85–115	i. Aled	12·6
	j. New Radnor	8·7
55–85	k. Knighton	8·6
	l. St. Asaph	7·3
Under 55	m. Overton	4·8

This association lends strong support to the view that the high gastric cancer mortality which exists in North Wales may be due to the high organic content of the soil over most of the area, and is fundamentally similar to the high mortalities from cancers of most sites that exist in the Fenlands; and that the difference in site-distribution between the two areas is a result of secondary factors—namely, specific gastric irritants that several writers have suggested exist in North Wales.

Discussion

The association of total cancer mortality with soil organic matter suggests that a carcinogen may exist in food plants grown on soils of high organic content, or, alternatively,

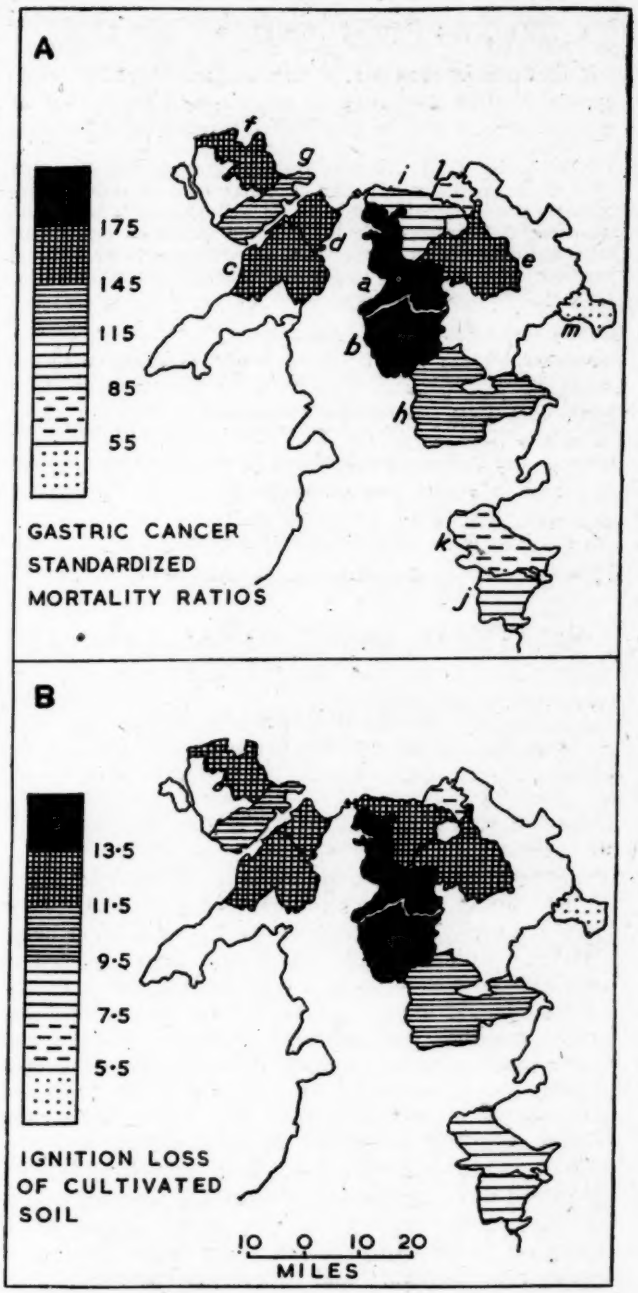

FIG. 2.—The rural districts are: a, Hiraethog; b, Penllyn; c, Gwrfai; d, Ogwen; e, Ruthin; f, Twrcelyn; g, Aethwy; h, Llanfyllin; i, Aled; j, New Radnor; k, Knighton; l, St. Asaph; m, Overton.

that a protective substance may be lacking in such plants. In view of the fact that copper deficiency sometimes occurs in crops grown on peat (although obvious copper-deficiency lesions have not been reported in England and Wales), brief reference may be made to copper metabolism.

Dawson and Nair (1950) have confirmed the power of soil organic matter to fix copper in a form that is unavailable to plants. It is probable, therefore, that plants and soil organic matter may compete for the copper present in the soil, and that the appearance of copper-deficiency diseases in crops is merely an extreme case.

Summary

It is suggested that the major geographical variations in cancer mortality in England and Wales are associated with variations in the organic content of cultivated soils,

and may be conditioned by micronutrient deficiencies in food plants grown on soils of high organic content; and that populations whose diets include vegetable foods grown on such soils may be subjected to the action of carcinogens, or may be deprived of protective substances.

I thank Mr. G. C. Worters for the original suggestion that total cancer mortality might be at a maximum on soils of high reducing power and at a minimum on well-oxygenated soils; and the General Register Office for granting access to unpublished statistical data. Most of the work on which the paper is based has been done during the tenure of a research studentship of the London School of Economics.

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BILATERAL GIANT RENAL CALCULI

BY

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Giant renal calculi have not infrequently been described in the literature, but only four weighing over 1 kg. have been reported, Pohl's (quoted by Legueu, 1921) being 2,005 g. Although such calculi have been reported in one kidney, accompanied by a small calculus in the other, bilateral giant renal calculi are rare. Morrison (1921) described the case of a man aged 50 who had a left renal calculus weighing 1,130 g., together with a smaller one on the right side. Everett (1934) described an example in a woman aged 59, in whom the right kidney contained a calculus weighing 622 g., while the left contained one weighing 329 g. Gutierrez (1939) described three cases. A further case is reported below. It demonstrates the extraordinary adaptation of which the kidneys are capable, and seems to be the largest example of bilateral renal calculi yet recorded.

Case History

The subject was one of a family of eight children, of whom one died in infancy, another of pulmonary tuberculosis at 25 years, while the other five are alive and well. His father was a small farmer who died of old age at 88. His mother died at 83 from a fractured femur. He was apparently well and free from illness until 15, when he began to experience recurrent attacks of pain in the abdomen and back, occurring at intervals of three to five weeks and lasting sometimes up to 24 hours. He developed an aversion to sitting down, as this tended to bring on the pain. His preference for spending his time engaged in some such pursuit as carpentry, instead of performing his milking duties with the other sons, for a time earned him the disapproval of his family and the reputation of a malingerer. Eventually a doctor was consulted. He was admitted to hospital for a month, during which time he was symptom-free. On returning home his symptoms recurred. He learnt to ease his pain during attacks by riding on a bicycle over rough ground as hard as he could. He became a butcher and also kept a smallholding.

At the age of 27 a large stone and some smaller ones were removed from one kidney at Guy's Hospital. To his great disappointment, however, the symptoms recurred as soon as he returned home. Thereafter he eschewed medical advice as much as possible. As time went by the attacks of pain became less frequent, but he experienced bouts of haematuria, and episodes when his urine became foul-smelling and offensive, presumably being heavily infected. A constant dull aching pain in the back developed. From the age of 45 onwards he attended his doctor infrequently for episodes of haematuria and urinary infection. Further operative treatment was advised but refused. At the age of 61 his doctor attended him for a severe bout of haematuria and found him to have easily palpable and very hard kidneys. His blood pressure was 210/100; he was obviously anaemic, yet managed to do his work. *X*-ray examination revealed enormous bilateral renal calculi. He would consent to no

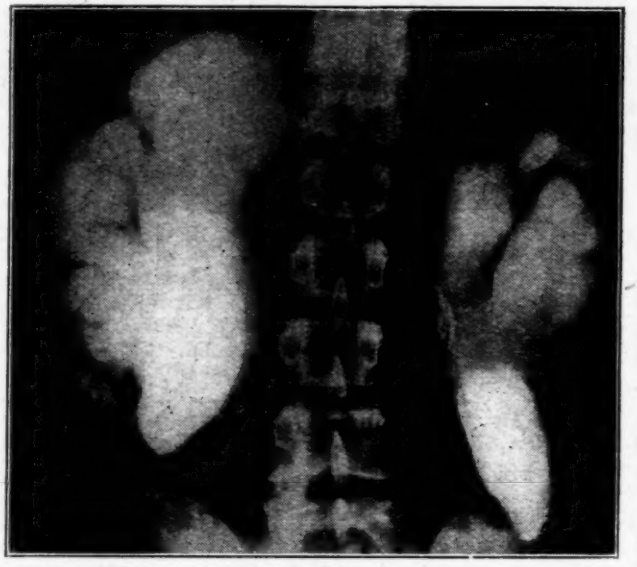

FIG. 1.—Radiograph showing large bilateral renal calculi.

further investigations, yet offered his kidneys for examination after his death. He experienced periods of sickness and headache, and usually had a brown furred tongue. He continued his work, smoking heavily and consuming a pint of beer daily until May, 1949, when, during a local influenza epidemic, he became ill with headache and a cough. After initial improvement he became drowsy and began to vomit; his urinary output fell, and he died 10 days after going off sick.

Specimens

The right kidney weighed 1,680 g. (see Fig. 2). It consisted of a thin shell of renal tissue covering an enormous coralliform calculus measuring approximately 19 by 10 cm. On hemisection, septa of renal tissue only 2 to 4 mm. in thickness were seen to extend down in between the stout processes of the stone. The renal tissue covering the stone varied from 1 to 3 mm. in thickness, except at those places from which the septa arose, where triangular areas of renal tissue were present, each having a base of approximately 1 cm. One ureter appeared to be a little thickened. The calculus was mostly white, was very hard, and resembled marble in appearance. In the lower part of what had once been the renal pelvis a central yellow and brown stone was present which appeared older than the rest. When freshly cut, laminations running parallel to the convex surfaces were visible throughout the calculus and fine radial markings were also apparent. Until cut the calculus was in one piece. The kidney (unfrozen) was clamped in a vice for cutting, a process which took about one hour with a hacksaw.

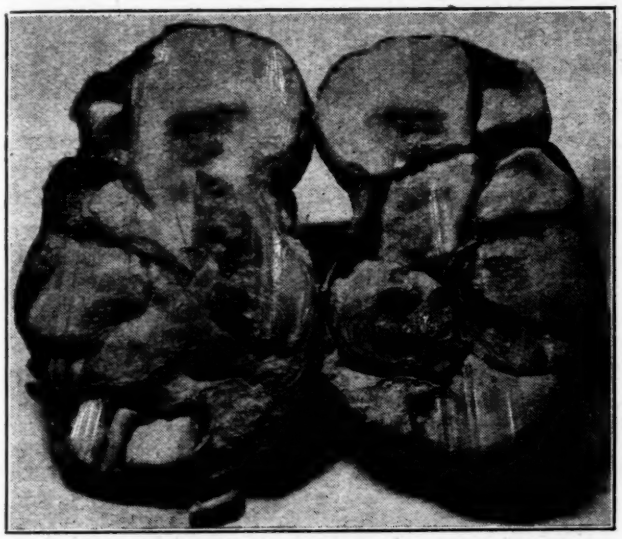

FIG. 2.—The calculus of the right kidney.

The left kidney weighed 720 g. and contained one main calculus measuring approximately 18.5 by 8 cm., together with several smaller calculi. The lower end of the main calculus extended down into an elongated portion of the renal pelvis and contained a laminated brown oval stone appearing older than the rest. The remainder of the main calculus extended in a coralliform fashion into dilated calices, leaving a narrow rim of renal tissue. The main portion of the stone was composed of a hard white laminated material possessing radial markings. A natural joint was present between the main calculus and another at the upper pole of the kidney. The surfaces of the joint were convex and concave, and were covered by a smooth thin layer which was denser and whiter than the subjacent stone. Several other smaller calculi were present in some calices. The rim of renal tissue varied in thickness from 2 to 10 mm. At the upper pole and on the lateral border were moderately sized areas of renal tissue 10 mm. in thickness. The ureter was only slightly thickened.

The calculi of both kidneys were composed of carbonates and phosphates. No trace of urates or oxalates was found even in the denser pelvic stones.

Microscopical sections from the recognizable areas of kidney substance in each kidney showed a flattened single layer of pelvic epithelium, separated by a layer of fibrous granulation tissue from functioning renal tissue. Most of the glomeruli showed thickening of the capillary basement membrane; a few were shrunken, but none were obliterated. In some areas the tubules were dilated. There was moderate interstitial fibrosis. The arteries were narrowed by thickening of the intimal connective tissue and by medial hypertrophy.

Summary

A case of bilateral renal calculi of exceptional size is recorded. Despite the distortion of the kidneys into mere rims of renal tissue thinly covering the calculi (a state which was shown by *x*-ray examination to have been present for at least three years), renal function had been adequate until the subject contracted a terminal acute respiratory infection.

Reference is made to other giant renal calculi recorded in the literature.

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PETHIDINE AND LIVER DAMAGE

BY

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Detoxication of pethidine by the liver has been proved by the animal experiments of Bernheim and Bernheim (1945). This has been verified by Way, Swanson, and Gimble (1947), who suggested that in patients with severe hepatic impairment the desired therapeutic effect of pethidine might be obtained with smaller dosage. A review of the literature has failed to reveal any case report to substantiate this view, and it is therefore felt that the following cases will prove of interest in support of the hypothesis.

Case Reports

Case 1.—The patient, a man aged 40, had a history of repeated haematemesis. Laparotomy in November, 1950, revealed a cirrhotic liver and splenomegaly. Liver biopsy showed early multilobular cirrhosis. Liver-function tests on April 19, 1951, gave the following results: van den Bergh, direct reaction, very feeble, delayed; serum bilirubin, 1.6 mg. per 100 ml.; serum alkaline phosphatase, 8.3 units per 100 ml.; serum colloidal gold, 5; zinc turbidity, 10 units; thymol turbidity, 5 units; thymol flocculation, ++++; cephalin cholesterol, ++++. Hippuric acid excretion was impaired. Urinary urobilinogen was present in dilution 1:40.

On May 1 splenectomy was performed under D-tubocurarine chloride, thiopentone, nitrous oxide, oxygen, and pethidine anaesthesia. The patient's condition was satisfactory at the end of operation, and morphine, 10 mg., was given on three occasions for post-operative sedation. Pethidine was administered in divided doses as follows: during operation, 100 mg.; first post-operative day, 100 mg.; second day, 200 mg.; third day, 400 mg.; fourth day, 200 mg. Up to the third post-operative day the patient's progress was satisfactory. That evening he became delirious and disorientated, a condition which was attributed to uraemia. The blood urea, however, was 39 mg. per 100 ml. His condition remained unchanged during the fourth day, when, on bearing in mind the possibility of drug intoxication, the pethidine was discontinued. The following morning he was much improved and was quite lucid. He had complete amnesia for the second to fourth post-operative days. His subsequent progress was uneventful.

Case 2.—A woman aged 25 had a history of subacute hepatic necrosis in 1943, and haematemeses on two subsequent occasions. Clinical examination revealed marked ascites, enlarged spleen, but unpalpable liver. On May 16, 1951, liver-function tests showed: van den Bergh, direct reaction, feeble, prompt; serum bilirubin, 1.6 mg. per 100 ml.; serum alkaline phosphatase, 15 units per 100 ml.; serum colloidal gold, 5; zinc turbidity, 9 units; thymol turbidity, 7 units; thymol flocculation, ++++; cephalin cholesterol, ++. Urinary urobilinogen was present in dilution 1:40. The A/G ratio (Howe's technique) was 1.05:1. On May 25 splenectomy and spleno-renal anastomosis were performed under D-tubocurarine chloride, thiopentone, nitrous oxide, oxygen, and pethidine anaesthesia. The operation lasted four hours, during which time 0.45 g. of thiopentone, 50 mg. of D-tubocurarine chloride, and 50 mg. of pethidine were administered. A frozen section of the liver showed a nodule of excellently regenerated liver tissue

lying in an area of old cirrhosis. For post-operative sedation the patient was given 100 mg. of pethidine at minimal intervals of six hours, 600 mg. being given in the first 48 hours. On the second post-operative day she became progressively more drowsy, there was marked nystagmus, and the pupils were widely dilated and just reacting to light. Pethidine administration was discontinued that evening, and the following morning she was fully conscious, although nystagmus persisted for a further 24 hours. There was complete amnesia for the first two post-operative days.

Case 3.—This patient, a man aged 32, was under treatment for primary syphilis. He had had 6.45 g. of neoarsphenamine and 15 g. of bismuth oxychloride during the previous nine weeks and was admitted to hospital with cellulitis, possibly due to an extravenous injection of arsenical. His liver was slightly enlarged and tender, and urinary urobilinogen was present in a dilution of 1:50, although he was not jaundiced. Because of generalized pruritus and pain he was given 400 mg. of pethidine in 24 hours, after which a collection of pus was drained under nitrous-oxide–oxygen anaesthesia. During the subsequent 24 hours 500 mg. of pethidine was administered and the patient became very delirious. Pentabarbitone, 300 mg., was given, but it only made the delirium worse, necessitating the administration of 7.2 ml. of bromethol, following which he slept for 12 hours. Slight delirium returned after this interval, but was again controlled by "mist. three-fifteens," composed of potassium bromide, 15 gr. (1 g.); chloral hydrate, 15 gr. (1 g.); tinct. opii, 15 min. (0.9 ml.); aqua chlor. to ½ oz. (15 g.). The following day he was quite lucid, with amnesia since before operation.

Case 4.—A man aged 30 had Banti's syndrome. Liver-function tests showed van den Bergh, direct reaction negative; serum bilirubin, 0.8 mg. per 100 ml.; serum alkaline phosphatase, 17 units %; serum colloidal gold, negative; zinc turbidity, 3 units; thymol turbidity, 6 units; thymol flocculation, negative; cephalin cholesterol, ++++. Splenectomy and spleno-renal anastomosis were performed under D-tubocurarine chloride, thiopentone, nitrous oxide, oxygen, and pethidine anaesthesia. The patient was induced with 20 mg. of D-tubocurarine chloride and 0.35 g. of thiopentone. During the remainder of the operation, which lasted 3 hours 15 minutes, a further 0.1 g. of thiopentone and 40 mg. of D-tubocurarine chloride, together with 50 mg. of pethidine, were administered.

Commentary

Cases 1 and 2 had a significant degree of liver-function impairment as demonstrated by recognized laboratory investigations. It was reasonable to suppose on clinical grounds that Case 3 had some degree of hepatic dysfunction (McLachlan, 1945).

In spite of the administration of pethidine in dosage not considered to be in excess of normal, the first three cases all showed signs of pethidine overdosage—namely, delirium and amnesia. A normal adult subject should tolerate 100 mg. of pethidine parenterally or orally every four hours (Batterman and Himmelsbach, 1943). Excessive dosage results in cerebral irritation, and widely dilated pupils and nystagmus have been reported as toxic reactions following overdosage (von Brücke, 1940). Cessation of toxic signs on withdrawal of the drug in these cases supports the assumption that they were due to the pethidine. These cases serve as an illustration of the fact that in the presence of liver damage toxic signs occur with therapeutic overdosage of pethidine.

Pethidine now holds a recognized place in anaesthesia. From the above one would not be surprised to find that patients with liver damage require much less pethidine than normal subjects to maintain satisfactory anaesthesia. This is illustrated by Cases 2 and 4. The average dose of pethidine during anaesthesia appears to be in the region of 25 mg. per half-hour (Mushin and Rendell-Baker, 1950; Johnson, 1951). The larger the dose of thiopentone used for induction of anaesthesia the smaller are the increments of pethidine required for its maintenance. With dosage of thiopentone of the order of that given in Cases 2 and 4 one would have expected to require a greater amount of pethidine than was actually administered.

Summary

Four cases of pethidine administration in the presence of liver damage are described.

Toxic reactions followed administration of normal therapeutic dosage in three of them.

Requirements of pethidine to maintain anaesthesia were less than normally anticipated in two of the cases.

These four cases support the hypothesis of Way *et al.* that in patients with severe hepatic dysfunction the desired therapeutic effect of pethidine can be obtained with smaller dosage.

We are indebted to Professor C. A. Wells for his helpful criticism and permission to publish these cases.

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Medical Memoranda

Extensive Intraperitoneal Haemorrhage of Unknown Origin

The cause of extensive intraperitoneal haemorrhage is usually obvious—such as ectopic pregnancy, spontaneous rupture of the spleen and liver, and ruptures of aneurysms and blood vessels. Excluding the obvious pathological and traumatic conditions, Brewer and Marcus (1948) report nine cases from the literature and add one of their own of intra-abdominal apoplexy in which no definite bleeding-point was found. A further case of interest is reported.

CASE REPORT

A married woman aged 44 had had one normal pregnancy 16 years ago. Her menstrual periods were normal, lasting three to four days, with a 25-day cycle. Her last period had occurred 18 days previously. Sharp spasmodic lower abdominal pain began on the day before admission and was increasing in severity. On the day of admission an apparently normal period started, although it was a week early. She had not had any morning sickness or noticed any breast changes. Her only past illness had been rheumatoid arthritis during the past ten years.

On examination she was seen to be very pale, wasted, and collapsed. Her temperature was 96° F. (35.6° C.), pulse 88, and respiratory rate 20. No abnormality was found in her respiratory and cardiovascular systems. Her abdominal movements were restricted and there was tenderness and guarding over the lower abdomen.

On vaginal examination the uterus was anteverted and normal in size. Pressure in the fornices caused extreme pain. An indefinite boggy mass was felt in the pouch of Douglas which suggested blood clot. On speculum examination blood was seen to be issuing from the external os. A diagnosis of intraperitoneal haemorrhage was made, and this was thought to be due to a ruptured ectopic pregnancy.

At laparotomy under general anaesthesia the abdomen was opened by a subumbilical midline incision and found to contain between 2 and 3 pints (1.1 and 1.7 litres) of blood and blood clot. The Fallopian tubes and ovaries were first palpated and then inspected, but no cause for the bleeding was found. The liver and spleen were next palpated, but no abnormality was observed in the upper abdomen except for a few filmy adhesions. Loops of intestine were drawn out and inspected. The abdomen was

mopped dry, but no indication of the cause of the bleeding was found. The left ovary and tube were adherent to the side wall of the pelvis, and their appearance suggested the development of an early endometriosis, so they were removed.

Meanwhile the patient was receiving a blood transfusion, as her condition was deteriorating. It was thought that she would not stand having the incision extended upwards for inspection of the upper abdomen, and as there was no further bleeding the abdominal wall was closed in layers. A large-bore rubber drainage-tube was left draining the abdomen, so that any further bleeding might be detected quickly. No further bleeding took place. The patient's condition improved after 2 pints (1.1 litres) of blood had been given, and her blood pressure rose from 60/40 to 100/75. The improvement continued.

The following are the results from blood investigations taken four days later: bleeding-time, 3½ minutes; clotting-time, 4½ minutes; haemoglobin, 85%; rhesus factor, "D" positive; white cells, 3,000 per c.mm.; Wassermann reaction, negative; Kahn test, negative.

The pathological report states that an early acute salpingitis and an acute peri-oophoritis were present. The lumen of the tube contained pus; the mucosal rugae, muscular coat, and serosa were infiltrated by polymorphs. The ovary contained a follicular cyst and a corpus luteum as well as a number of small cysts lined by columnar epithelium just beneath the surface. These cysts had resulted from peritoneal metaplasia due to peri-oophoritis.

The patient made an uneventful recovery, and was well when seen two months later.

I am indebted to Mr. Vivian H. Barnett for permission to publish this case.

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Obstruction of the Urethra by Sulphamerazine Crystals

Numerous cases of sulphonamide anuria have been recorded since the first report by Smith *et al.* (1940). Southworth and Cooke (1939) and Tsao *et al.* (1939) had previously reported marked oliguria, but had not appreciated the significance of it. This form of anuria is due to obstruction of the lower end of the ureter by a sludge composed of epithelial debris and possibly some crystals of the drug. In the male infant a similar obstruction can occur in the urethra, and, although it is apparently not a rare occurrence, it has as yet received little attention.

Rice-Edwards (1950) reported a case of retention of urine due to a collection of crystals in the urethra following the administration of "cremomerazine." Ellison Nash (1951) mentions this complication of sulphamerazine therapy in children and states that it may occur after four-hourly administration of the drug. The following case is reported in detail to draw attention to this complication and to emphasize the simple precautions necessary when administering sulphamerazine to children.

CASE REPORT

A boy aged 3 years and 10 months and weighing 2 st. 13 lb. (18.6 kg.) was admitted to Southmead Hospital under the care of Dr. Beryl Corner and referred to the genito-urinary department. He had developed pneumonia three days before admission, and this had been treated by sulphamerazine in the form of cremomerazine. Forty-eight hours after starting the course of treatment the child developed acute retention of urine, and had passed no urine for 24 hours before admission.

His mother stated that she had been instructed to give the child two teaspoonfuls of cremomerazine four-hourly, and had been supplied with enough for three days—that is, a 4-oz. (114-ml.) bottle, which contained 12 g. of sulphamerazine in suspension. She admitted that rather more than two teaspoonfuls had been given at each dose and that the bottle was emptied in less than 36 hours. The child had therefore received 12 g. of sulphamerazine in that time. His past medical history revealed nothing abnormal other than slight chronic bronchitis following whooping-cough 18 months previously.

On admission he was in great distress, with a tense distended bladder. The whole penis was swollen, and by separating the oedematous lips of the external urinary meatus a whitish paste could be seen in the urethra. A probe was inserted just inside the meatus and a small amount of the paste was dislodged. The child immediately passed about 50 ml. of urine, but the flow was then cut off with intense strangury, leaving the bladder still distended.

He was taken to the theatre and a general anaesthetic administered. The paste was removed by passing a fine rubber catheter through which the urethra was continuously irrigated with sterile water. It took three to four minutes to clear the penile urethra; then the catheter passed easily into the bladder and 150 ml. of opalescent fluid was withdrawn.

The oedema of the penis was less next morning, but did not disappear for two days.

The urine from the bladder was examined and found to contain sulphonamide crystals and large quantities of amorphous debris. Specimens of urine were collected at six-hourly intervals, and it is of interest to note that crystals were still present in the specimens taken six and twelve hours after operation in spite of a copious fluid intake and administration of alkalis.

COMMENT

The cause of this obstruction appears to be similar to that of obstruction of the ureter in adults, except that in the child there are more crystals and less epithelial debris in the sludge. The urethra in the male infant is so small that it can be blocked by sludge more readily than the ureter. It will be noticed that the point at which the sludge impacts is in the distal part of the penile urethra just before it opens out to form the navicular fossa.

Cremomerazine is a palatable suspension of sulphamerazine and is particularly suitable for children. It is easily administered and is a great asset to the doctor in general practice. However, like all other suspensions of sulphonamide drugs, it is not perfect and if allowed to stand even for a few hours a sediment will appear in the bottle. Unless the bottle is thoroughly shaken before each dose is given, the quantity of sulphamerazine received by the patient is apt to be increased as the bottle is emptied.

The dosage recommended for children of from 3 to 10 years of age is two teaspoonfuls—that is, 1 g. of sulphamerazine—every 12 hours. The interval of 12 hours is emphasized on all bottles supplied. It will be noticed that in our case the child was given two teaspoonfuls every four hours, making three times the recommended dose. Owing to the relatively slow excretion of sulphamerazine, an adequate blood level can be maintained with 12-hourly doses. If, however, it is given four- or eight-hourly, like most other sulphonamides, the dose must be reduced accordingly

The further precautions necessary when administering this drug are those common to all the sulphonamide group. An output of at least 1,500 ml. of alkaline urine a day in an adult (less according to age) should be aimed at.

Usually a probe inserted in the external urinary meatus is enough to dislodge the sludge and promote a free flow of urine, but urethral irrigation may be necessary.

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Reviews

SHOCK

Physiology of Shock. By Carl J. Wiggers, M.D., Sc.D., F.A.C.P. (Pp. 459; 56 figures. £1 12s. 6d.) Harvard: University Press. London: Geoffrey Cumberlege. 1952.

Dr. Carl Wiggers's new book on the cause of shock will be warmly welcomed by many investigators. During the last 40 years his group have published more than 50 papers on shock and haemorrhage. The book has evolved from these. But it is far more than a monograph on the experimental findings from a single laboratory, though these are of great importance. Dr. Wiggers touches on every major contribution from the earliest times up to 1948; each is appraised impartially and nicely displayed in its right perspective. So the grateful reader obtains, perhaps for the first time, an admirable and authoritative overall impression. He will not begrudge the fact that some passages make rather difficult reading.

After describing the approaches to the problem up to the second world war he considers the aetiological and symptomatic aspects of clinical shock and concludes that its development is often caused by a considerable reduction in blood volume. In the following chapters he discusses the production of experimental shock in animals, especially haemorrhagic shock. The resulting alterations of function in the cardiovascular system are then portrayed in great detail. In the progressive stage, the reduction of venous return is due to trapping of blood in the minute vessels rather than to loss of fluid by increased permeability. The explanation of this is not settled. The myocardium is also impaired. The effects on respiratory, oxidative, metabolic, and many other functions are also considered. The author ends by indicating the probable direction of future investigations.

HENRY BARCROFT.

ENDOSCOPY

Endoscopy as Related to Diseases of the Bronchus, Oesophagus, Stomach, and Peritoneal Cavity. By Edward B. Benedict, M.D., F.A.C.S. (Pp. 373; 130 figures. £3 17s. 6d.) London: Baillière, Tindall and Cox. 1951.

This book is attractively produced and beautifully illustrated. There is an interesting introduction on the history of endoscopy and the experiments and difficulties of the early instrumentalists. Each section on bronchoscopy, oesophagoscopy, and gastroscopy opens with an excellent description of the anatomy and physiology on which the technique is based. It is a pity that the author does not go straight on to describe, in the light of his great experience, the appearances that may be seen, the deductions that may be drawn from them, and the errors that may be made. Instead, there follows in each section a catalogue of diseases, some very rare, in which endoscopy might be done. The occurrence, aetiology, treatment, and prognosis of each condition are listed under these subheadings even when the relevance of endoscopy is slight. The preface and foreword suggest that this approach to the subject is deliberate—with the object of making the endoscopist into a clinician. But the result is a synopsis of certain diseases from the endoscopic point of view which are more objectively discussed in standard textbooks of medicine, while the points the author wants to make about endoscopy become rather obscured. This is unfortunate, because some of these points are of great importance—for example, the necessity of insisting on bronchoscopy in a case of haemoptysis, in face of a negative *x*-ray examination of the lungs.

In Britain we tend to have our clinicians first, and encourage them to develop such endoscopy as they need. For British students the book could with advantage have been smaller and confined to the subject indicated by the title.

HERMON TAYLOR.

FLUID BALANCE

Fluid Balance: A Clinical Manual. By Professor Carl A. Moyer, M.D. (Pp. 191. £1 8s.) Chicago: The Yearbook Publishers, Inc. London: Interscience Publishers. 1952.

Carl Moyer, professor of surgery at Washington University School of Medicine, St. Louis, has made notable contributions in the last decade to the subject of this book, and what he writes may be accepted as sound. His declared aims are practical: to present a simple scheme of diagnosis concerning abnormalities of fluid and electrolyte balances and to give practical advice on treatment. He has succeeded in achieving his intentions.

The book begins with a brief review of outstanding historical publications. Particularly interesting are his quotations from the writings of O'Shaughnessy in 1831 on the blood changes in cholera and the letter from Dr. Latta, of Leith, on his remarkable trial of the administration of copious intravenous fluid in 1832. Professor Moyer then goes on to explain the composition and equilibrium of the body fluids and the causes and effects of their main disturbances. There follow interesting chapters on the evaluation of clinical and laboratory data in states of fluid and electrolyte imbalance. The final portion of the book is on treatment and the complications of fluid therapy. Much of what is said is generally known, but there are many interesting original observations and fresh points of view. This manual is well worth reading by all interested in the subject.

H. L. MARRIOTT.

TRAUMATIC SURGERY

Die Technik der Knochenbruch-Behandlung. By Dr. Lorenz Böhler. Volume 1. 12th–13th edition. (Pp. 1,151; 1,721 figures. M. 98.) Vienna: Wilhelm Maudrich. 1951.

The appearance of the twelfth edition of Böhler's great work on fractures is sufficient evidence of its popularity and of the unique position which Professor Böhler holds in this field. The vast experience which lies behind it is shown in the fact that it is based on a study of nearly half a million injuries and of a million and a half radiographs. But the work would be more correctly described as a treatise on traumatic surgery, for the author discusses wounds and injuries of every description, in which a fracture is often only a minor consideration.

The present volume is on general problems in the treatment of injuries, and the principles involved in treating open wounds, correcting deformities, and supporting fractures. Professor Böhler discusses them in great detail and describes their application both in civil injuries and in war. He then considers fractures of the skull, of the vertebral column, and of the upper limb, but includes with this a full account of injuries of the head and face, of the trunk, and of the arm and hand. The book is very fully illustrated and every possible contingency is carefully considered. It is indeed a magnificent work, and those who are not familiar with German will be grateful to know that there is now a new edition in English.

HENRY SOUTTAR.

CHEST RADIOLOGY

Chest X-ray Diagnosis. By Max Ritvo, M.D. (Pp. 558; 615 illustrations on 418 engravings and a coloured plate. £5 5s.) London: Henry Kimpton. 1951.

Although this purports to be a textbook on chest *x*-ray diagnosis, and is written by a radiologist, a very considerable proportion of it is devoted to descriptions of clinical and pathological aspects of disease. For instance, in the section on silicosis three and a half pages are devoted to clinical and pathological aspects, and one and a half pages, together with a table, to radiological aspects. No detailed description of radiological appearances is given, nor is there any large-scale illustration of the characteristic patterns of

opacity in the various forms of pneumoconiosis. Perhaps it is not reasonable to expect these long clinical and pathological sections to reach the standard required for a clinical or pathological textbook, but clarity and accuracy at an elementary level can be expected, and these are not attained. Other evidence of lack of balance is afforded by the relative prominence given to various subjects. Radiographic technique in examination of the lungs is described in five pages; there is no discussion of the criteria by which the adequacy of chest films may be judged, nor of the adjustments in technique which are required to correct faults in the films. Pulmonary tuberculosis, which is queerly linked in one chapter with histoplasmosis, receives 20 pages, and lung abscess four pages, whereas berylliosis and sarcoidosis each receive five pages.

In the preface, the author states that one of the purposes of the book is to make available a large and varied collection of radiographs. Certainly there are more than 400 radiographic illustrations, but their quality is very variable, and in some instances the interpretation of them is open to question. To take only two examples, Fig. 37, which is presented as an example of atelectasis of the right lower lobe, suggests in the reproduction a patchy bronchopneumonia involving the right lower lobe, together with a scoliosis; and Fig. 38, which is labelled "Atelectasis, right middle lobe," shows atelectasis of both the right middle lobe and the anterior segment of the right lower lobe. The inadequate scale of some of the reproductions of radiographs has already been mentioned.

In any book of this size, criticisms in matters of detail can always be made, but the occasion for them is far too frequent in this book. As a term for increased translucency to *x* rays the extraordinary word "radiability" is used alternatively with "radiance." If it is thought desirable to have a special word applicable to *x* rays and analogous to translucency, "transradiancy" seems the most acceptable neologism. There are many other evidences of careless writing. For instance, "virus and rickettsial diseases involving the lungs" are included among the differential diagnosis of virus pneumonia. There are also many inaccuracies in matters of fact. "Jaagstekte" [*sic*] is described as a virus disease of sheep which rarely occurs in humans, and which gives rise to alveolar cell carcinoma. It is stated that pneumonia frequently develops in chicken-pox. Siderosis is defined as a lesion which occurs in workers with metals, particularly metallic oxides. The bone changes in sarcoidosis are described as "closely similar to those in leprosy." The nomenclature of the bronchial tree given on p. 34 and that in Plate 1 do not agree with each other. Although a fairly extensive list of references is given at the end of each section they are predominantly to the American literature. This insularity of outlook may be illustrated further by the observations that in the section on Q fever no mention is made of its occurrence in Australia, let alone of its original description in that country; and that in the discussions of oesophageal abnormalities and hiatus hernia there is no reference to the work of Allison and his colleagues in Leeds. This book cannot be recommended.

J. G. SCADDING.

LABORATORY TESTS

Clinical Laboratory Diagnosis. By Samuel A. Levinson, M.S., M.D., Ph.D., and Robert P. MacFate, M.S., Ph.D. Fourth edition, thoroughly revised. (Pp. 1,146; 221 illustrations and 13 plates, 10 in colour. £4 4s.) London: Henry Kimpton.

This book has been brought up to date by including accounts of the newer tests of the functions of the liver and suprarenals, flame photometry, and methods for detecting incomplete Rh antibodies. The chemical section includes almost all the useful methods of investigation. Descriptions of methods are clear and detailed. The only criticism is that the authors might have given a better indication of the relative values of different investigations; for example, all the tests of liver function given on p. 102 are not equally useful. The haematology section is less satisfactory. The Westergren sedimentation tube is not mentioned, and most pathologists in this country have given up the correction of the Wintrobe result for the degree of the patient's anaemia. The problem of blood-group nomenclature is handled well, but in a work of this size discussion of the laboratory tests used in the diagnosis of haemophilia could well have been expanded.

Descriptions of the bacteria are given in the form of an elaborate table. This is not a very satisfactory method, since it is difficult to give adequate emphasis to the really important bacteria; no mention is made of the mitis, intermediate, and gravis types of diphtheria bacilli. Few bacteriologists would agree with the author that boiling water for 30 minutes will kill all spores. In spite of some defects, however, the book is a useful source of information which would be difficult to find elsewhere and should be useful to the pathologist in training. It is hardly a work for the medical student.

J. R. MARRACK.

PSYCHOSURGERY

Psychosurgery in the Treatment of Mental Disorders and Intractable Pain. By Walter Freeman, M.D., Ph.D., F.A.C.P., and James W. Watts, M.D., F.A.C.S., F.I.C.S. Second edition. (Pp. 598; 156 figures. £3 17s. 6d.) Oxford: Blackwell Scientific Publications. 1951.

This, the second edition of Freeman and Watts's pioneer monograph on prefrontal leucotomy, is enlarged in proportion to the increased experience of the authors. In 1942 they reported on under 100 cases. In the present volume this figure has been increased by over 400, of which the majority are schizophrenics. When the first edition appeared Watts had operated on only 12 cases of schizophrenia. The results obtained with the present series of 228 cases are essentially the same as those reported by other workers—a reduction in distress in the great majority of cases and a resumption of some sort of social effectiveness in about a third of those operated on.

Of the new material the most fascinating is the report on the surgical treatment of behaviour disorders in children. Although the results are not encouraging, they indicate that the abnormal child is unexpectedly tolerant of frontal-lobe damage, which apparently causes no gross impairment of learning ability or deterioration in behaviour. All these children are described as schizophrenics; while this is quite possibly correct, this chapter underlines all three of the major defects of the book. First, the authors appear to lack psychiatric sophistication—that is to say, the diagnostic groups are mainly descriptive and consist essentially of those patients showing disturbed behaviour (schizophrenia), those who are depressed (affective disorder), and those who are over-anxious and over-conscientious (the obsessive-compulsive group). Secondly, the material is not presented in detail or summarized in a way which would enable the reader to draw conclusions of his own. Most provoking is the continual reference to an interesting point in, say, case 336; detailed search in the index and text fails, however, to disclose any further reference to this patient. Thirdly, the authors do not often relate their own results to those of other workers. Even Freeman's own results with the "ice pick" method are only briefly noticed. As a consequence this is neither a textbook on leucotomy nor a source of material for the research worker. The book remains a readable and stimulating record of the individual work and rather naive opinions of two American doctors who had the enthusiasm and technique to adapt and popularize Moniz's original operation. There can be no doubt about the value of their work, and their original book is of historic importance in psychiatry. Although beautifully produced and lavishly illustrated, the present edition is not worth twice the money.

ALICK ELITHORN.

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THE BACTERIOLOGICAL DETECTIVE

The Jenner Memorial Lecture by Brigadier J. S. K. Boyd which we print in this issue describes an aspect of present-day laboratory work with which the profession as a whole is not yet fully familiar, although its results have been invaluable. The laboratory has for many years been able to help the epidemiologist by confirming the presence or continuance of a specific infection in patients and in particular in carriers. What it has not been able to do until more recently has been to distinguish between one strain of the same species and another, and thus to confirm, for example, that a given carrier is in all probability the source of an infection in certain patients. It is now possible to identify with a high degree of certainty individual strains among several bacteria commonly causing epidemic disease, and it should be a source of satisfaction that most of the work which has made this possible has been British.

The distinguishing characters by which "types" can be recognized within a species are of three quite different kinds. Perhaps the least satisfactory are cultural—colonial form and fermentative capacities—but these distinguish the three main types of diphtheria bacillus, and the recognition of even these three is of far from negligible value in epidemiological studies. The characters which have served to differentiate other species are antigenic, and from the epidemiological point of view the outstanding work in this connexion is that of the late Frederick Griffith on the antigenic differences among haemolytic streptococci. He was able by means of the agglutination test to classify strains from human infections into 30 different types. The service thus rendered to the elucidation of the spread of streptococcal infections was immense. It became possible for the first time to prove the source of a case or outbreak of puerperal fever. Prolonged ward epidemics of illness with a variety of manifestations and previously unsuspected of being the result of cross-infection could be explained. Re-infection with another type of streptococcus was shown to be the cause of complications in scarlet fever, and milk-borne outbreaks of this disease could with certainty be traced to their ultimate source. The significance of these advances has been obscured by the facility with which streptococcal infection can now be suppressed by chemotherapy.

There are other species which can be subdivided in neither of these ways. The typhoid bacillus is subject to no variations in either cultural characters or antigenic constitution which enable one strain to be distinguished from another. It was for this species that phage-typing, the subject of the Jenner Memorial Lecture, was first brought into fruitful use. Susceptibility to lysis by different phages now serves to distinguish no less than 36 types of typhoid bacillus. The types responsible for all the epidemics of typhoid fever in this country for some time past are known, and it is immediately possible by ascertaining the phage type of an organism from a case or carrier to determine its probable connexion with an epidemic or to prove the contrary. Boyd describes the first application of the method in this country: this showed that the disease in a laboratory technician had not been acquired in the laboratory, since it was due to a type of typhoid bacillus not maintained there. He also tells again perhaps the most remarkable story in which this method has been used: how scattered cases of typhoid fever in the Home Counties were all traced to a single carrier, a farmer in Wiltshire, whose intermittently contaminated milk, which was mixed with that from other farms, went to households in five different counties. Without type identification it would have been difficult even to suspect and quite impossible to prove that this obscure source was responsible for so many cases of typhoid fever occurring over a period of nearly two years. It is no exaggeration to liken this specific type of typhoid bacillus, appearing in a number of widely scattered areas, to the finger-prints of a criminal. Boyd also gives an account of how he applied phage typing to studying the epidemiology of typhoid fever in the Middle East during the war, showing that different armies and population groups had disease caused by distinct types of organism.

What can be done with typhoid bacilli is now also possible, although on a more restricted scale, with paratyphoid bacilli and at least two members of the food-poisoning group. Although the method is being applied to several other bacteria its results have been most useful in the investigation of infections caused by staphylococci, of which a large number of phage types have now been defined. In tracing a particular source of infection the method, as applied to this organism, has been most useful in outbreaks of food-poisoning. It is possible for a single infected person or carrier to contaminate food served to large numbers of people, and several instances of the identification of such a source and its verification by typing have occurred during the past few years. Not long ago food-poisoning among passengers in the "Flying Scotsman," in people lunching in restaurants in the City of London, and in guests at a wedding feast in Suffolk was traced to a single source—a supply of cold meat served at all these meals. Two employees of the firm which prepared the pressed beef

and brawn concerned were both nasal carriers of the incriminated type of staphylococcus, and one had a septic finger. The typing of staphylococci has also served to explain the occurrence of infection in both infants and mothers in maternity hospitals, although here it has not so much verified a single source of infection as proved that the responsible strain has extensively colonized the staff of the institution. The facility with which a penicillin-resistant type of staphylococcus, notably that designated as 52A, can establish and maintain itself in such institutions (its regular habitat being the noses of the majority of the nursing staff) is one of the major unsolved problems in epidemiology at the present day.

All who have seen this method at work and consequently know the value of the precise and detailed information which it can provide will agree that these refinements in technique rival, if they do not surpass, any method employed in criminology. There need be very few unsolved problems in the epidemiology of these infections in the future, and the extension of the method to other forms of disease and its application in other ways foreshadowed in this lecture may be expected to yield further valuable results.

THE DISTRIBUTION SCHEME

The Working Party's scheme for the redistribution of the central pool has drawn, as our correspondence columns have shown, some of the fire of criticism which any proposals of such importance must expect. In contentious matters of this kind critics tend to go wide of the mark, and Dr. Charles Schiff's assurance[1] is to be welcomed when he says, "I certainly did not for one moment intend to suggest that the members of the negotiating body or of the G.M.S. Committee were actuated by other than the purest motives in pursuing the course they considered best for the profession."

Letters received over some weeks have shown that the points of criticism of the Working Party's scheme remain substantially unchanged. Young practitioners, or those speaking for them, have been the chief complainants. They want bigger incomes for the small-list beginner and smaller incomes for the big-list man. They complain that the position of those practitioners least favourably placed under the present distribution will be relatively worsened instead of improved. They think that the distribution scheme does not encourage partnerships sufficiently and that it favours too much the man who is a permanent employer of assistants without a view.

Faced with the infinite variety of general practice and its practitioners, those who had the task of distributing £10m. in the best interests of general practice (so far as remuneration was concerned) had a far from straightforward problem to solve, for any distribution scheme was bound to leave some recipients unhappy. In healthy competitive medical practice—and without competition the healthiness of general practice would be in doubt—there always must be, and always has been, an element of fortune, but this element is less now than when there was no distribution scheme to take the blame for financial hardship. A simple and, in the minds of some, a fair solution would be an even, all-round increase of the capitation fee. Such an arrangement would at least be in accordance with the sound principle of relating pay to responsibility and work done. The solution of the Working Party, bound as it was to its terms of reference and to the recommendations of the Spens Committee, had to be more complex. It accepted the further restriction of lists and so a restriction of the earnings of the hard-working big-list practitioner; it tried to help the unestablished young practitioner, and to give the greatest encouragement to a middle group with lists of average size. Whatever opinions the critics may hold of the likely effects of the Working Party's scheme, they are wrong to suggest that the welfare of the young practitioners has been neglected. These should remember that their interests are bound up with the advancement of general practice as a whole. A sound practice is not static, and to rob the Peter of the good established practice to subsidize the Paul of the unestablished practice would be to deprive general practice and its future practitioners of much healthy enterprise. It would, in fact, encourage the salaried-service mentality.

As reported in this week's *Supplement*, the General Medical Services Committee at its meeting on September 18 decided, in the light of the rider passed by the special conference[2] of local medical committees on June 26, to set up a subcommittee to investigate the position of any groups of practitioners who may not benefit as intended from the recommendations of the Working Party, and to suggest such remedies as may be necessary. In addition, local medical committees are to be asked to report any special cases in their areas. A year's experience of the scheme in practice will give the answer to many questions, particularly in regard to the effect it will have in encouraging partnerships.

CORONERS' INQUESTS

Most doctors at some time during their career find themselves giving evidence at that curious survival of mediaeval England, the coroner's inquest. The origin of the coroner is lost in the Dark Ages. It is said by some that the office existed in England before the Norman conquest. It certainly existed in the time

[1] *British Medical Journal Supplement*, September 13, p. 129.
[2] Ibid., July 5, p. 1.

of Henry I and has continued ever since. Coroners' rights and obligations are now regulated principally by the Coroners Acts of 1887 and 1892 and the Coroners (Amendment) Act, 1926. Coroners have never existed in Scotland. Many people hold that in England they have outlived their usefulness and should be abolished.

The coroner's principal duties are to inquire into the cause of death of persons found dead within his jurisdiction when there is reasonable cause to suppose that death was either violent or unnatural, or was sudden and of an unknown cause; to hold inquests upon treasure trove; in the City of London to hold inquests upon the outbreak of fires; and to act occasionally in place of the sheriff. Until 1938 it was he who pronounced judgment in outlawry. It is only in connexion with the first of these duties that coroners, except on the rarest occasions, now function.

The object of the inquest, therefore, is to inquire into the cause of death, and accordingly it is the duty of the coroner to receive any evidence of this that he can find, as it is the duty of anyone who knows anything which may cast light on the cause of death to offer evidence to the coroner. In practice, statements are taken by the coroner's officer from anyone who is likely to be able to help, and these, together with the pathologist's report, form the basis of the coroner's oral examination of the witnesses at the inquest.

Interested parties, such as the relations of the deceased or his employers, and particularly anyone who may be blamed for the death, are entitled to attend the inquest, though the coroner has a judicial discretion to exclude the public or any individual. It is established practice that counsel or solicitors should be allowed to attend and examine or cross-examine the witnesses, though they do so only by the coroner's leave and are not allowed to make speeches except by dressing them up as cross-examination.

Unless the death has been caused by negligence on somebody's part so gross as to justify a verdict of manslaughter, it is no part of the coroner's duty to apportion blame or to investigate responsibility for the death except in so far as such an investigation is unavoidable in investigating its cause. But the inquest affords interested parties such as the relatives of the deceased an excellent opportunity for eliciting the facts surrounding the death and getting them recorded in the depositions while they are fresh in the witnesses' minds. This may be of great value in later civil proceedings arising out of the death, for in these the depositions can be used to cross-examine a witness who has changed his story. Although, therefore, the coroner should not be interested in civil responsibility for the death, the cross-examination at an inquest is generally and often vigorously devoted to allocating blame and fishing for negligence. A not uncommon result is that the coroner's jury, a body of men drawn from a field not restricted by the modest qualifications required by jurors at assizes or quarter-sessions or in the High Court, adds a "rider" in which it allocates blame or recommends remedies to prevent recurrence of disasters it thinks should have been avoided.

Two things are certain about a coroner's jury's rider: it is in law no part of the verdict; and it will be reported in the Press. Here it may often cause grave and undeserved damage to reputation, and the victim has no redress. Riders have become a feature of inquests which, though their origin is obscure, is now hallowed by tradition. What a rider is, and why a jury should be allowed to make it when it is no part of the verdict which it is the jury's function to return, is incomprehensible.

The coroner's inquest is a matter which no doctor called to give evidence before it should take lightly, since he is open to the potential danger of a damaging rider by the jury. Whether this danger can be abolished without the abolition of the whole system may become clearer when the report of the interdepartmental committee on the scope and duties of coroners courts is published.

FIELD RESEARCH ON CANCER PATHOGENESIS

As more and more carcinogenic agents are being identified, the possibility that malignant growths in some parts of the body are initiated by substances continually being ingested or inhaled in small quantities cannot be ignored. Studies of occupational mortality have shown that cancer of the oesophagus—and also of the larynx, mouth, and rectum—occurs more often than among the male population generally in groups of men whose occupations are usually associated with regular and heavy drinking, and that bladder tumours arise with notable frequency among men who have worked for long periods with certain chemicals handled in the manufacture of dyes. The statistical evidence is now very strong that bronchogenic carcinoma is connected with the inhalation of carcinogenic substances present in tobacco[1] and in the smoke from domestic chimneys,[2] though the nature of these carcinogens has yet to be established. Elsewhere in this issue we publish an interesting paper by Mr. C. D. Legon, who has found that in some areas of the country a high mortality from cancer is associated with a high content of organic matter in the soil.

It was first shown in the Registrar-General's occupational mortality analysis of 1921–3[3] that the incidence of cancer of the stomach among men must be influenced

[1] Doll, R., and Hill, A. B., *British Medical Journal*, 1950, **2**, 739.
[2] Stocks, P., *Brit. J. Cancer*, 1952, **6**, 99.
[3] *Registrar General's Decennial Supplement*, 1921, "Occupational Mortality and Fertility," 1927, London.
[4] *Registrar General's Decennial Supplement*, 1931, "Occupational Mortality," 1938, London.
[5] Stocks, P., *Regional and Local Differences in Cancer Death Rates*, Studies on Medical and Population Subjects, No. 1, 1947, London.
[6] Stocks, P., *Brit. J. Cancer*, 1950, **4**, 147.

strongly in some way by social and environmental factors; and the more comprehensive study of deaths in 1930–2[4] showed that this was true also of married women. No such relation with social factors was found for cancer of the intestines. In a series of papers appearing in the annual reports of the British Empire Cancer Campaign for 1936, 1937, and 1939 Stocks pointed out that, whereas standardized death rates during 1921–30 for cancer of the stomach in the counties and towns of England and Wales showed pronounced geographical variations and were greatly affected by urbanization, this was not the case for cancer of some other sites such as the intestines and breast. This was confirmed by later studies,[5] and the possibility that differences might arise from local peculiarities in certification of causes of death was subjected to a number of tests, which in fact failed to lend support to such an idea.[6] Differences between the large towns and within London county are almost as pronounced as regional contrasts in rural death rates. There is a remarkable disparity in death rates from gastric cancer in the rural districts of North Wales and those in South-east England, but no inverse relation between mortality attributed to gastric cancer on the one hand and to diseases which might be mistaken for it on the other appears in these two areas. Furthermore, in Switzerland, where geographical variation of gastric cancer mortality is just as pronounced, experts are not of the opinion that this can be explained away by peculiarities in certification of the cause of death.

The high certified mortality from gastric cancer in North Wales deserves very careful study, and the local organization of the British Empire Cancer Campaign began in 1939 to plan an investigation to discover the reasons for it. After delays caused by the war and much discussion and consultation, a field study designed to last five years—more comprehensive than the original plan in that it covers all forms of cancer—is now in progress throughout five counties of North Wales, the Liverpool hospital region, and the Isle of Man, a compact area showing extreme contrasts in living conditions. Dr. Percy Stocks, who was appointed to a senior research fellowship by the British Empire Cancer Campaign, is directing the work, in which the Liverpool and Welsh Regional Hospital Boards, the Radium Institutes in Liverpool and Manchester, the medical officers of health in the research area, and the Department of Agricultural Chemistry in the University College of North Wales are all co-operating. The aim is to ascertain, as far as may be possible, the environmental histories of persons resident in the area and found to have any form of primary malignant neoplasm, leukaemia, or lymphadenoma. Inquiries will cover the 20-year period prior to onset of the disease, but with such matters as tobacco-smoking attempts will be made to obtain the whole life history. The items covered by the inquiry include places of residence and work; occupations; travel to work; heating, cooking, and lighting in the home; sources of vegetables and milk; water supply; customary diet; and tobacco. Special attention is being directed to soil, subsoil, and the use of fertilizers. The information, which of course is voluntarily given, is regarded as confidential and for statistical use only. Follow-up of any kind during life is strictly excluded, and linkage of a hospital record with a subsequent death record of the same person takes place only within the statistical office.

Although complete coverage of every case of cancer in the area is not essential for many purposes of the research, one of the aims is to work out the true incidence of the disease in the research area. Success in this will depend on the full co-operation of the surgeons, who are not always easily persuaded that statistics can ever throw light on pathogenesis. The natural objections of hospital staffs to "another form" is being met in part by payment of a small fee to cover clerical help. It is to be hoped that the success of this research will not be imperilled by that lack of co-operation on the part of a few which is proving a handicap to cancer registration in some areas. Registration is concerned with treatment and not with pathogenesis, but it has this in common with the North Wales research, that every case not recorded through lack of interest on the part of a minority detracts from the ultimate value of work being done willingly by all the others. Cancer poses the most difficult and urgent problems in preventive as well as curative medicine. Up to the present time too little field research has been done upon it, so no effort should be spared to help the British Empire Cancer Campaign in this venture.

INSPIRED MILLIONS

At the beginning of this century, when there was an outcry for the liquidation of millionaires—a process which economic evolution has now gone far to complete—someone suggested that a better alternative would be to inspire them. The records of two outstanding inspirations have now appeared almost simultaneously in the shape of the reports of the Rockefeller and of the Nuffield Foundations.[1] [2] The object of these Foundations, one based on New York and the other on London, is, expressed in the widest terms, to promote the welfare of mankind. The Rockefeller Foundation was chartered in 1913; the Nuffield is of much more recent origin—the present report being the seventh. Both, while giving financial assistance over a wide field of the sciences and humanities, place public health in the forefront of their objects. Of the income of nearly 17 million dollars of the Rockefeller Foundation in 1951, almost one-fourth was spent on public health and medical sciences. What were known as the International Health Division and the Medical Sciences Division of the Foundation have been merged, and the combined operation is focused on four aims: the advancement of professional education; the study of medical care; the investigation and control of specific diseases; and the development of public health services. In medical education it is not the Rockefeller plan to distribute largesse for buildings and endowments, but rather to make relatively modest grants at strategic points. Medical care has been a main

[1] *The Rockefeller Foundation: A Review for 1950 and 1951.* By Chester L. Barnard. President of the Foundation. New York.
[2] *The Nuffield Foundation: Report for the Year ending March 31, 1952,* Oxford University Press.

interest of the Foundation for more than two decades; at the moment it takes the form of studies in rural communities in the United States, where special attention is being paid to what is called the "biosociology" of disease and health. The report states—not quite accurately so far as British medical schools are concerned—that the schools demand no knowledge of the relation of social conditions to the health of the individual, and that the old idea that biophysics and biochemistry will eventually unravel the problem is still too dominant.

The Nuffield Foundation is working on a five-year plan which is due to be completed in 1954. This plan gives prior attention in the United Kingdom to medical, biological, and sociological research. One important part of the work, under the name of the Oliver Bird Fund, is the study of rheumatism. Work is proceeding here along various lines at different centres, but the frank admission is made that all that is clear at the moment is that the key to the rheumatic problem still remains to be discovered. Another feature of the Nuffield programme concerns the care of old people. Nearly five years ago the Foundation set up a body called the National Corporation for the Care of Old People for the purpose of encouraging voluntary bodies to help the aged. But apart from this measure of pure benevolence important research in ageing is being carried out with the encouragement of the Foundation at the psychological laboratory at the University of Cambridge. One line of research concerns the capacity of various industries to absorb or retain some of their older workers. Certain forms of employment lend themselves in a special way to the assimilation of elderly workers. It is not suggested that there is a single solution applicable to all jobs in all conditions; a series of interlocking solutions will have to be found, and success will depend very largely upon the attitude of the younger as well as the older workers and of the trade unions and managements concerned. Studies of ageing are also engaging the interest of the Rockefeller Foundation. A grant has been made to the University of California for the making of physiological and psychological measurements of ageing; and in New York City, where there are 600,000 citizens of 65 and over, a pilot study is being undertaken of the human adjustment problems presented by this segment of the population.

One important note is struck in the Nuffield report, and finds some echo in a rather different connexion in the Rockefeller report, concerning the preservation of freedom of research. The Nuffield report raises the question whether, with the increasing proportion of university income now derived from central government sources—and this will presently reach three-quarters of the total income of the universities—there is any threat to the traditional independence of academic work and the freedom of the universities to arrange their own affairs. Perhaps the threat is hardly discernible as yet, but the possibility makes all the more important the comparatively much smaller, but alternative, resources which private trusts like these can offer for the support of such speculative activities as research.

PRE-DIABETES

The existence of a pre-diabetic state is a relatively modern concept deriving much support from the observation of abnormalities in the obstetric records of women who ultimately develop diabetes. Elsewhere in this issue Dr. W. P. U. Jackson joins the ranks of those workers who have reported the birth of large babies and a high foetal loss rate in pre-diabetic women, and who have found a number of undiagnosed diabetics amongst women who have had large babies or stillbirths. There can be no doubt that some factor operates in the pre-diabetic woman to cause overgrowth of the foetus and a high foetal loss rate for many years before clinical diabetes develops.

There is still much speculation on the nature of this factor. Jackson mentions the popular hypothesis which claims that the overgrowth of the foetus and the subsequent maternal diabetes are both caused by an overproduction of somatotrophin by the maternal anterior pituitary. An obvious objection to this hypothesis lies in the fact that acromegaly is very rare in the pre-diabetic woman. It seems that we must await the development of an efficient method for the assay of somatotrophin in body fluids before the validity of this hypothesis can be proved.

The theoretical importance of the concept of the pre-diabetic state is obvious, but, as Jackson suggests, it is small consolation to the diabetic woman to know that she has passed through this state. Nor is there much practical value in being able to predict the development of clinical diabetes in a patient if we can do little, apart from weight reduction, to prevent the inexorable advance of the disorder. But, should an effective method of prevention be discovered, the recognition of the pre-diabetic state would be of the greatest importance.

At present there are no means by which a definite diagnosis of pre-diabetes can be made. We know that certain circumstances, the birth of large babies and a high foetal loss rate, are premonitions of a possible diabetic future. To these we may have to add hydramnios and toxaemia of pregnancy, and if there is a family history of diabetes and the patient is obese the premonitions become virtual promises. The minor changes in carbohydrate tolerance which Jackson considers to be pre-diabetic tend to be inconstant in the individual and are of doubtful significance. Much more long-term study will be required before we can assess the risk of the development of diabetes in any one patient. At the same time it will be necessary to search for other signs which will increase the accuracy of our prognosis.

Jackson's observation that pre-diabetic fathers beget big babies is also of much interest and destroys the complacency with which we have hitherto blamed the mother alone for the overgrowth of her foetus, though apparently she is still responsible for the high foetal loss rate. It is to be hoped that further studies of the pre-diabetic state in the father will soon be made.

We announce with regret the death on September 19 of Dr. Alexander Edward Gow, emeritus physician to St. Bartholomew's Hospital.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

DISSEMINATED SCLEROSIS

BY

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Disseminated sclerosis is one of the commonest neurological diseases in the United Kingdom and occurs rather more often in women than in men. The most frequent time of onset is between the ages of 15 and 30, but a considerable number of patients first have symptoms between 30 and 50, and occasionally the disease starts after the age of 50.

Diagnosis

This remains essentially a clinical problem, and little help can be obtained from pathological investigations except by the exclusion of other conditions in difficult cases. It is the evolution of the disease which gives the clue to the diagnosis, and typically there is evidence in the history of episodes of neurological disorder occurring at varying intervals of time and involving different parts of the nervous system, while on examination the physical signs indicate more than one lesion.

In taking the history very careful inquiry is necessary about the possibility of an earlier episode, as this may have been of short duration and forgotten by the patient, or some non-committal diagnosis such as neuritis, food-poisoning, or a nervous breakdown may have been given him. These early incidents are of various types: a common one, occurring in about 25% of cases, is a unilateral retrobulbar neuritis with dimness of vision in one eye coming on over the course of a few days, sometimes accompanied by pain on movement of the eyes, normal vision returning in three to four weeks or less.

Other early symptoms about which inquiry should be made are double vision lasting for a few days, weakness of one or more limbs often accompanied by numbness or tingling but not by pain, a severe attack of vertigo and vomiting without tinnitus or deafness, and difficulty in walking which lasts for a few days. When a history of one or more episodes of this type, sometimes occurring many years previously, can be obtained from a patient who has physical signs of involvement of the pyramidal, cerebellar, or sensory pathways, a diagnosis of disseminated sclerosis can usually be safely made. When, however, the patient is seen in the first episode with an uneventful previous history, and the physical signs can be accounted for by a single lesion in the nervous system, there may be considerable doubt about the diagnosis except in the case of unilateral retrobulbar neuritis, which, in the United Kingdom at any rate, is nearly always due to disseminated sclerosis. In cases of this type the course of the disease will usually clarify the diagnosis either by the appearance of lesions in other parts of the nervous system or by the patient making a symptomatic recovery. Patients who have persistent symptoms and physical signs should be investigated more thoroughly and kept under regular observation so that more potentially treatable conditions, such as myasthenia gravis, neurosyphilis, subacute combined degeneration of the cord, and cerebral or spinal tumours are not overlooked.

Physical Signs

As would be expected from the disseminated and variable distribution of the plaques in the central nervous system, physical signs vary considerably from case to case, and also at different times in the same patient. In retrobulbar neuritis, which is common as an early symptom, but may also occur at later stages of the disease, the visual acuity is reduced but the optic disk is often normal, although in a minority of cases there is unilateral papilloedema. Testing of the visual fields by confrontation will, however, always show a central scotoma with a full peripheral field. In patients with temporary uselessness of an arm it is common to find impairment of position sense and of stereognosis, but cutaneous sensation is usually normal.

The pyramidal tracts tend to be involved early in the disease whether it advances by relapses and remissions or by gradual deterioration without remissions, and this results in a variable degree of spasticity and weakness with increased jerks and extensor plantar responses. The abdominal reflexes disappear at an early stage; this is a sign of some importance, as in certain other conditions affecting the pyramidal tracts—in particular, amyotrophic lateral sclerosis—the abdominal reflexes may be retained in spite of very brisk tendon jerks and extensor responses. Posterior column sensation, especially appreciation of vibration, also tends to be reduced in the early stages of the disease. Lower motor neurone lesions, with wasting and absent tendon jerks, are of great rarity, and if these are present a diagnosis other than disseminated sclerosis is probable. The really important finding is physical signs which cannot be accounted for by a single focal neurological lesion or by a systematized tract degeneration.

There are three groups of physical signs which at times have been overemphasized in the diagnosis of disseminated sclerosis. The first is Charcot's triad of nystagmus, intention tremor, and scanning speech. These are signs of cerebellar dysfunction which may occur with various pathological processes. They may of course occur in disseminated sclerosis, but only in a relatively small proportion of cases and then often in the late stages of the disease. The second is bitemporal pallor of the optic disks: the colour of the normal disks varies considerably from person to person, the temporal side usually being paler than the nasal, and pathological pallor is often very difficult to assess. Unless there is a history of retrobulbar neuritis or impairment of visual acuity with visual field changes, considerable care should be taken in the assessment of temporal pallor. The third of the groups is euphoria, which is said to be common in disseminated sclerosis: this is a quality difficult to estimate unless one knows the patient well, and certainly many sufferers from the disease are not euphoric. Though euphoria may occasionally be present, a much commoner finding, especially in the later stages, is emotional lability, and at times pathological laughter and crying.

The patients in whom diagnosis is most difficult are those, frequently over the age of 40, in whom there is slow but steady progress of symptoms, such as a spastic weakness of the legs with minimal sensory involvement, or a slowly progressive hemiparesis without evidence in the history or

physical examination of disseminated lesions, and in these patients further investigation is necessary. In the patient with slowly progressive weakness of the legs the blood Wassermann reaction and a lumbar puncture are necessary, and if the Queckenstedt response gives any indication of spinal compression, or if the protein content of the cerebrospinal fluid is raised, a myelogram should be carried out. With a progressive hemiparesis *x*-ray examination of the skull, the blood Wassermann reaction, and a lumbar puncture will be needed, and possibly an air-encephalogram to exclude a cerebral tumour.

The Cerebrospinal Fluid

The common finding in disseminated sclerosis is a normal fluid. In about 30% of cases the lymphocyte count is raised to about 10 per c.mm., and occasionally up to 40–50 per c.mm. The protein content is raised to 50–100 mg. per 100 ml. in a similar proportion of cases, and is very occasionally over 100 mg. per 100 ml. The most striking abnormality is a first-zone, or "paretic," Lange gold curve, which occurs in about 25% of cases; when this is found with an otherwise normal cerebrospinal fluid and the Wassermann reaction is negative in both the blood and the cerebrospinal fluid, and there is no history of antisyphilitic treatment, it is important confirmatory evidence of the diagnosis.

Prognosis

This is a matter of considerable difficulty in any individual case in the early stages, as there are three different ways in which the disease behaves. (1) There may be a series of relapses and remissions with, in general, the relapses becoming more severe and lasting longer on each occasion; during remissions the patient may have no disability, but residual signs such as absent abdominal reflexes and extensor plantar responses may persist. The length of remission varies from a few weeks up to 20 or more years, and it is probable that there are occasional patients who have one or two attacks and then remain symptomless for the rest of their lives. (2) In some patients there is a slow but steady progress of the disease, sometimes punctuated by periods of slight improvement, but a complete remission never occurs. (3) There is a small group of patients in whom the disability progresses to a certain stage of disability, which may be slight or severe, and then remains stationary for many years.

In general, a remitting course is usual when the disease starts before the age of 35–40, and a slowly progressive course without remissions when it starts above this age, but there are exceptions to this. Attacks of acute onset are more likely to remit than those which start gradually, while involvement of cranial nerves, in particular retrobulbar neuritis, or of sensory pathways more often recovers completely than does involvement of the pyramidal or cerebellar pathways. Once an attack has persisted for six months a notable remission is improbable.

In exceptional acute cases with a plaque in the brain-stem, death may result from respiratory failure, but the common causes of death in the chronic cases are respiratory or urinary infections or toxaemia from bed-sores, while a number of patients die of some coincidental disease. It has been estimated that the average duration of life is about 20 years from the onset of the disease.

Management and Treatment

In early cases it is generally advisable not to tell the patient the name of the disease, as "popular" medical books are apt to be consulted and a uniformly gloomy prognosis assumed, which may well be wrong in the individual case. The patient who recovers from an attack of retrobulbar neuritis or a temporary paralysis of a limb who is told that she has disseminated sclerosis, and who then waits for the next attack of the disease and eventual complete incapacity, when in fact she may have many years of good health or minor disability, presents a dismal spectacle. It is usually, however, advisable to explain the situation more thoroughly to a responsible relation and to give warning of the probability of relapses.

Treatment in bed is needed only in severe acute episodes of the disease and in severely disabled chronic cases who cannot be looked after otherwise. Other patients are better not confined to bed, particularly those with ataxia of the legs, who often become more ataxic when kept in bed. Fatigue aggravates symptoms and should be avoided so far as is possible, but, in general, patients should continue at work when this is at all practicable, as this is important from the point of view of morale. Febrile illnesses cause temporary aggravation of symptoms in many patients, and sufferers from the disease should take a cold in the head or influenza more seriously than normal people and not try "to fight it off" by continuing at work, but should have a few days in bed. There has been a general impression that relapses tend to occur in pregnancy or in the puerperium, but recent follow-up studies have not confirmed this as a general rule, and disseminated sclerosis is not in itself a good indication for termination of pregnancy. It must, however, be remembered that the care of an infant may be a serious extra burden for a woman partially disabled by the disease.

Medicinal Treatment

The effects of treatment are notoriously difficult to assess in a disease which has spontaneous remissions, but it is generally agreed that no drug treatment known at present has any effect in arresting the course of the disease. Many drugs have, of course, been employed: arsenic has for long been used empirically, given by the mouth as liq. arsenicalis 3 minims (0.18 ml.) in solution three times a day for six weeks at a time, or by weekly intravenous injections of 0.45 g. of neoarsphenamine, six to eight injections being given in a course; but toxic reactions may occur with neoarsphenamine and chronic arsenic poisoning with liq. arsenicalis. Other substances which have been used include copper, gold, dicoumarol, and tetraethylammonium bromide, but all these are potentially dangerous and have no definitely beneficial effect. In a condition in which there is no reliable evidence that any medicinal treatment can alter the course of the disease it is unwise to use a potentially dangerous drug, and it is preferable to employ as a placebo some substance that will not harm the patient; it is in this category that liver injections and quinine have been used, the former in 2-ml. injections once a week in courses lasting eight weeks, the latter as iodobismuthate of quinine, 1 ml., given by deep intramuscular injection weekly for a similar period. Fever therapy, induced either by intravenous injections of increasing doses of T.A.B. vaccine or by a Kettering hypertherm, has been employed in treatment; but results are far from encouraging, and some patients, especially those with bulbar or sphincter disturbance, are worse after this method of treatment.

Symptomatic Treatment

Physiotherapy, especially re-educational walking exercises for ataxic patients, is of real help—in particular in re-establishing confidence and in helping them to make the best possible use of their disabled limbs.

Urgency of micturition is common in patients with bilateral pyramidal involvement, and this can often be helped by ephedrine, ¼ gr. (32 mg.) twice a day, by a pill containing dry extract of belladonna ¼ gr. (32 mg.), and extract of hyoscyamus 1½ gr. (0.1 g.), or by a tablet containing ergot, belladonna, and phenobarbitone. Less commonly, retention of urine or retention with overflow occurs, and in these patients carbachol, 2 mg. by the mouth six-hourly, may be helpful.

Spasticity is a common cause of difficulty in walking in patients in whom reasonably good muscular power remains,

but unfortunately it is difficult to influence this. Injections of curare in peanut oil have been tried, but these are very uncertain in action and are not to be recommended. Mephenesin acts as a depressant of spinal cord reflexes, and theoretically should be helpful in reducing spasticity, but in practice it is usually impossible to give a dose large enough to achieve this without producing toxic symptoms. In a minority of spastic cases, however, it is of some value, and should be given orally as the elixir, starting with one drachm (3.5 ml.) six-hourly, and increasing the dose gradually to three drachms (10.5 ml.) six-hourly if giddiness and double vision are not produced as evidence of overdosage. With a spastic foot-drop, a toe-raising spring is often helpful in preventing the patient constantly catching his toe on the ground when walking. In the later stages of the disease, when flexor spasms frequently bother the patient at night, a cradle should be put over the legs to prevent contact with the bedclothes, as this contact may initiate the reflex flexor spasms, and a barbiturate sedative given.

Epileptic attacks and paroxysmal trigeminal neuralgia occasionally occur as symptoms of disseminated sclerosis. The epileptic attacks can be controlled by the medicinal treatment used for idiopathic epilepsy as described in an earlier article in this series (*British Medical Journal*, 1950, 2, 1047), and trigeminal neuralgia responds as well as does the idiopathic variety to alcohol injection of the Gasserian ganglion or operative section of the sensory root of the fifth nerve.

Next Refresher Course Article.—"Interpretation of Wounds," by Dr. F. E. Camps.

A GERIATRIC UNIT IN A GENERAL HOSPITAL

BY

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With the approval of the Sheffield Regional Hospital Board a geriatric unit was formed in 1949 at the City Hospital, Nottingham. As associations with other hospitals and with statutory and voluntary bodies engaged in the care of the elderly developed, the local set-up began to conform to the plan for an area geriatric service proposed by the Special Committee of the British Medical Association on the Care of the Elderly (1947). The "lines of communication" were established, but free movement along the lines was restricted by insufficient accommodation at all points. Following the outlines of the plan of the B.M.A. Special Committee a diagram of the geriatric scheme in Nottingham and district is here given.

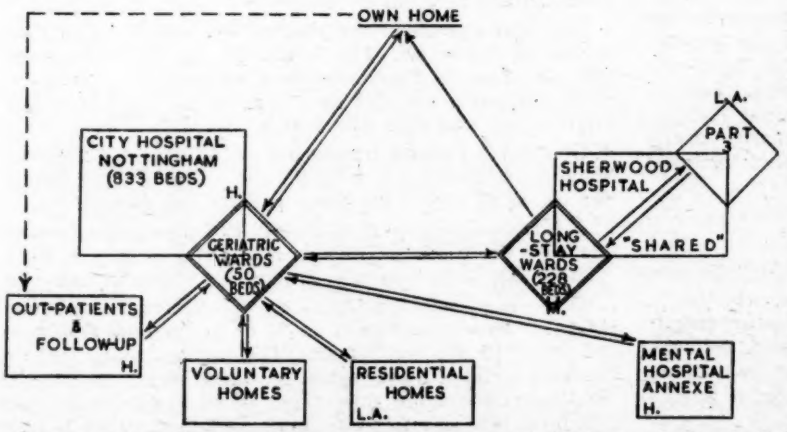

Diagram of the geriatric scheme in Nottingham and district. H=Hospital. L.A.=Local authority.

Central Geriatric Unit at the City Hospital

The City Hospital is a general hospital for acute cases. It has 833 beds and a full complement of consultant staff, special departments, etc. There are two "acute geriatric" wards, one for men and one for women, each of 25 beds. To these wards are admitted medical cases of pensionable age (men over 65, women over 60), but there is no absolute age bar, and patients under pensionable age with long-term illness may be accepted. On the other hand, no attempt is made to deal in the geriatric wards with all elderly medical cases referred to the hospital. In the year reviewed 74% of the men but only 49% of the women of the total medical admissions to the hospital of pensionable age were admitted to the geriatric wards. The avoidance of any suggestion of a "closed shop" policy undoubtedly contributed to the general acceptance of the experiment.

The geriatric wards are equipped with parallel bars for walking exercises, several beds have Balkan beams with slings, and the simpler instruments of physiotherapy such as wax baths are available. The only other furnishings not usually found in general medical wards are specially designed armchairs. Each ward has a small day-room.

Medical, Nursing, and Ancillary Staffs.—A consultant physician is in charge and is assisted by a medical registrar (shared) and a house-physician. A psychiatrist visits weekly and the services of other consultants are available when required. Each ward has a sister or male charge nurse, a staff nurse, a variable number of student nurses, and four or five ward orderlies. The almoner prepares a brief case history for each admission, and this forms part of the patient's medical record. Before discharge each case is discussed with the almoner, who has interviewed patients and relatives. Physiotherapy in the aged requires encouragement rather than electricity, and most of the treatments given are in the form of walking and other remedial exercises. Under the guidance of a physiotherapist many of the early day-to-day treatments are given in the ward; later the patients attend the physiotherapy department. Other ancillary services include occupational therapy, speech therapy, and chiropody.

Out-patient and Follow-up Clinics.—The scope of the geriatric out-patient clinic is restricted because of difficulty in transporting elderly patients; also, many are referred to the general medical and surgical clinics for specialist's advice. Nevertheless, 30% of patients referred have been treated as out-patients. Patients are seen at intervals of three to six months after discharge from hospital. Elderly patients enjoy revisiting the hospital, and get a feeling of added security from the continued interest in their cases. Moreover, this service appears to be appreciated by their general practitioners. The cause of failure to keep a follow-up appointment is investigated by the almoner.

Admissions

All cases are initially admitted to an "acute" geriatric ward, with the exception of those requiring long-stay accommodation transferred from another ward or hospital. There are four channels of admission:

(*a*) *Emergency Admissions.*—The wards "receive" two days a week for medical emergencies of pensionable age. This relieves pressure on the general medical wards.

(*b*) *From Waiting-list.*—The waiting-list is kept by the records officer, and is compiled mainly from requests from general practi-

tioners. Priority of admission depends on the combined medical and social need, and is decided by the physician-in-charge. In the first year 479 patients were admitted to the two acute wards. Of these, 135 were emergency admissions, including a number of social emergencies. The remaining 344 were admitted from the waiting-list. Throughout the year the waiting-list for women held from 10 to 35 names, and the delay in admission varied from one to eight weeks. For men the waiting-list was small and the delay only 2 to 10 days. Domiciliary visiting, which Brookes (personal communication) and Amulree *et al.* (1951) have found to be valuable, was not attempted. There has not been enough medical staff to undertake the work involved. Where home conditions rather than medical urgency appeared to predominate, reports of social conditions were obtained from the health visitors of the medical officer of health's department. In some cases, by arranging for the home help service, "meals on wheels," etc., it has been possible to continue to care for the patients at home. Information has also been obtained from the welfare department. If a welfare officer requested urgent admission, every effort was made to find a bed for the patient quickly.

(*c*) *Transfers from Other Hospitals and Wards.*—Usually these are patients likely to require hospital care for the remainder of their lives, and as they already have been investigated they are admitted direct to the long-stay hospital.

(*d*) *Readmissions.*—Priority is given to requests for readmission. Often a promise is given to relatives at the time of discharge that the patient will be readmitted if it is found to be too difficult to care for him or her at home.

Long-stay Wards at Sherwood Hospital

Sherwood Hospital is a separate but neighbouring hospital. Previously a local authority institution, the local authority has retained 242 beds as Part 3 accommodation. In addition there are 366 hospital beds; of these, 160 for women and 68 for men form part of the geriatric unit and receive transfers from the acute geriatric wards at the City Hospital, the remainder being under the care of two general physicians, who also transfer patients from their acute wards. Medical and ancillary medical staffs are obtained from the City Hospital, and the same geriatric "team" covers both institutions.

Sherwood Hospital has its own nursing staff of sisters, assistant nurses, and orderlies. Including night duty, the ratios are one trained nurse to 40 patients, and one State-enrolled assistant nurse or orderly to four patients. Initially, 95% of the patients were bedfast, 55% are now up, many fully dressed. There is insufficient accommodation for all those who get up, a number of whom are awaiting transfer to hostel or Part 3 accommodation.

Psychiatric Cases

Possibly because of an active mental health service, not many true senile dements come the way of the geriatric unit, but if an elderly psychotic is admitted it is usually found possible to transfer him or her to a mental hospital annexe, which, although not under the hospital management, is within the hospital grounds. Similarly, elderly patients there who no longer require psychiatric treatment can be discharged to the long-stay wards.

Discharge from Hospital

To Hostels (Local Authority).—Several hostels have been established; others will be available in the near future. There is good liaison between the geriatric service and the welfare departments of the local authorities, but the available hostel accommodation is quite insufficient for the numbers of elderly hospital patients no longer in need of hospital treatment but in need of care and attention.

To Old People's Homes.—There are several homes run by voluntary bodies. Again there is co-operation between the management of the homes and the physician and almoners of the geriatric unit; but the homes are full, and their occupants are often singularly hearty, so that few vacancies occur for patients discharged from hospital.

To Own Home.—Most of the patients discharged return to their own home or to the home of a relative. It has been found that the earlier the discharge the easier it is to arrange. When relatives began to realize that patients were admitted because of illness which might be only a temporary illness, and not because of old age, they became more willing to accept responsibility for the aged patients when fit to leave hospital. The use of the word "chronic" is banned. It is unfortunate that the Ministry of Health still uses the titles "chronic wards" and "chronic hospitals," names which will always be associated with the Poor Law infirmaries. Those who live alone often require more help than they did before admission to hospital, and many require such help for the remainder of their lives. This places a heavy burden on the Home Help Organization, but without home helps many more would have to remain in hospital. The "meals-on-wheels" service also is of great value, and could be extended with advantage. Also there is need for a home-laundry service. Apart from organized aid, voluntary or statutory, the almoner frequently has to depend on the co-operation of the patients' neighbours. It is reassuring to find that some good neighbourliness still exists.

To Convalescent Homes.—There is difficulty in finding vacancies for elderly patients in suitable convalescent establishments; this is partly due to lack of sufficient convalescent accommodation and partly to the unwillingness of some existing homes to accept elderly persons.

Results

In one year (August 1, 1949, to July 31, 1950) 250 men and 229 women, a total of 479, were admitted to the acute geriatric wards. The number discharged, dead, or remaining (including those transferred to Sherwood Hospital), and the average duration of stay, are shown in Table I.

TABLE I

	Men			Women			Total
	No.	% of Total	Average Stay	No.	% of Total	Average Stay	
Discharged	90	36	36 days	65	29	43 days	155
Died ..	81	32	16 ,,	70	30	15 ,,	151
Remaining	79*	32	27 ,,	94*	41	34 ,,	173

* Includes two men and four women transferred to a mental hospital.

Approximately one-third died, one-third were discharged, and one-third required long-term hospital care. Of the 155 patients discharged, 134 went home, 19 to local authority hostels, and 2 to voluntary homes.

The fatal cases had the shortest average stay: 26 died within 48 hours and 111 within 14 days of admission. Because of social conditions some were admitted virtually to die; others might well have been left to spend their last hours or days in their own homes.

Of the 173 patients transferred to the long-stay hospital, some were discharged, others died; obviously the longer the period of review the fewer patients will remain.

A further classification of the 479 patients admitted within the year was made six months later, on February 1, 1951. The results, in five-year age groups, are shown in Table II.

Only 46 patients (including six transferred to a mental hospital) remained—that is, 9.6% of the number admitted; of these, 18 are incontinent. The largest group, both of admission and of those remaining, was of women of 80 years and over, and more than twice as many women as men required long-stay hospital accommodation. Had it been possible to find vacancies in hostels or Part 3 accommodation this number would have been smaller. These figures

TABLE II

Age in Years	Men				Women			
	No. Admitted	No. Discharged	No. Died	No. Remaining	No. Admitted	No. Discharged	No. Died	No. Remaining
-64	35	21	12	2	30	15	12	3
65-69	53	30	19	4	28	20	6	2
70-74	65	31	32	2	60	21	30	9
75-80	56	20	34	2	36	13	17	6
80-	41	10	27	4	75	22	41	12
Total	250	112	124	14	229	91	106	32
% of Total	—	44·8	49·6	5·6	—	39·7	46·3	14

are very similar to those given by Professor Thomson (1949) at the Western Road Hospital, Birmingham—namely, discharged, 44%; died, 49%; remaining, 7%—but his review covered a period of 26 months against the 18 months of this series. The figures published by Mr. Cozin (1949) show a smaller percentage of discharges and deaths, but as they include a larger proportion of patients already belonging to the long-stay hospital group they are not exactly comparable.

Disease Classification

In elderly geriatric patients multiple disease is the rule rather than the exception, and it is extremely difficult to give a classification of the ailments. However, by taking as principal disease that which led to admission to hospital, it is possible to make a rather crude analysis. This is given in Table III, classified under the main headings of the *Manual of the International Statistical Classification of Diseases* (1948, World Health Organization).

TABLE III

	Analysis on February 1, 1951			
	No. Admitted	No. Died	No. Discharged	No. Remaining
Tuberculosis/respiratory	3	1	2	—
Neoplasms	31	24	6	1
Diabetes	8	2	6	—
Diseases of the blood	4	2	1	1
Central nervous system	123			
(*a*) Vascular lesions		49	48	11
(*b*) Other lesions		4	10	1
Circulatory system	198			
(*a*) Heart disease		98	44	8
(*b*) Hypertensive disease		11	17	6
(*c*) Disease of arteries and veins		7	7	—
Respiratory system	44			
(*a*) Pneumonia		10	6	—
(*b*) Bronchitis and emphysema		7	20	1
Digestive system	12	—	12	—
Genito-urinary	15	9	5	1
Arthritis and rheumatism	27	4	18	5
Senile dementia	3	—	—	3
Transferred to mental hospital (and still there)	6	—	—	6
Fractures and injuries	5	2	1	2
Total	479	230	203	46

Heart disease formed the largest single group, also the group with the highest mortality. The second largest came under the heading central nervous system, which included 101 cases of cerebral thrombosis; of these, 45 died, 45 recovered sufficiently to return home, and 11 remained. As was to be expected, there was a large number of men with bronchitis and emphysema, but more women with arthritis.

The numbers remaining in long-stay wards are too small for detailed analysis; nevertheless, they indicate a disease incidence similar to that reported in reviews of "chronic" hospitals. Analyses have been published by McEwan and Laverty (1949) and by Greenwood (1949), and these are compared with the present findings in Table IV.

TABLE IV

	Central Nervous System	Circulatory System	Arthritis, etc.
McEwan and Laverty	26·8%	12·6%	12·3%
Greenwood	25·5%	12·0%	9·5%
Present series	26·0%	30·0%	11·0%

The higher percentage of cardiac illness in the present series can be explained by the large number who died soon after admission, not living long enough to become "chronic."

After admission, investigation, and treatment in a general hospital a percentage of cases of cardiac failure, hemiplegic patients without recovery of power or with continuing incontinence, the fixed arthritics, and cases of advanced senile dementia still require prolonged care in a hospital, but the numbers requiring long-term treatment should be very much smaller than they have been in the past.

Summary and Comments

A geriatric unit of 50 "acute" beds for the admission, investigation, treatment, and classification of elderly medical patients established in a general hospital is described. Associated with this unit is an adjoining long-stay hospital and a mental hospital annexe, and there is liaison with voluntary and local authority homes and hostels.

Beds in both the general and the long-stay hospitals are under the charge of the same consultant physician, who is assisted by a team of almoners, physiotherapists, occupational therapists, a speech therapist, and a chiropodist.

Out-patient and follow-up clinics are held.

Patients are admitted as emergencies and as transfers from other wards or hospitals and from the waiting-list.

The waiting-list is kept at the central unit and is compiled from general practitioners' requests and transfers from other hospitals. Priority of admission is decided by the physician on combined medical and social needs.

Many beds in the long-stay hospital are blocked either by patients no longer in need of hospital treatment or by "chronic" cases inherited from the past. The present need is for greatly increased hostel accommodation for the ambulant aged, and for annexes where care, short of skilled nursing, can be given.

The results of the first completed year are analysed. Altogether 479 patients (250 men, 229 women) were admitted to the 50 beds of the unit in the general hospital. The largest single group was that of women of 80 years and over.

Of the total admissions, approximately one-third died, one-third were discharged, and one-third were transferred to the long-stay hospital.

Of the patients who were transferred to long-stay wards within eighteen months, only 46 (14 men and 32 women) remained. This was less than 10% of the total admissions to the geriatric unit during the year.

A classification of diseases shows that cardiac disease, hemiplegia, arthritis, and mental deterioration were the principal sources of long-term illness requiring prolonged hospital treatment. This corresponds to the findings reported from classifications of patients in existing chronic hospitals.

I wish to express my gratitude to the members of the medical, nursing, and ancillary staffs who have worked so enthusiastically

in both acute and long-stay wards; and my thanks to Mr. Tromans, records officer, and Miss King, for their long-suffering but willing co-operation in the compilation of this report.

ADDENDUM.—Since this report was completed, figures for the year August 1, 1950, to July 31, 1951, have become available. Total admissions to the two "acute" geriatric wards were 590 (290 men, 300 women) compared with 479 in the previous year. The most significant change was that 46% of the women were discharged against 39% in the first year.

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SECOND INTERNATIONAL CONGRESS OF INTERNAL MEDICINE

SCIENTIFIC SESSIONS

The scientific meetings of the Second International Congress of Internal Medicine, held in London from September 15 to 18 under the presidency of Sir Russell Brain, took place at Friends House, Euston Road. The sessions took the form of symposia.

I.—THE SPRUE SYNDROME

On Monday, September 15, Dr. NANNA SVARTZ (Stockholm) took the chair for the first of the scientific sessions, which was on the sprue syndrome.

The opening speaker, Professor C. D. de LANGEN (Utrecht), reviewed the theories of production of steatorrhoea. He thought that too much attention had been paid to the disturbances of fat metabolism. His own observations had shown that there was also deficient absorption of other bowel contents—namely, vitamins, metabolites, water, and gas. It was wrong to assume that meteorism arose from bacterial fermentation and excess gas formation. It seemed likely that there was inadequate absorption of gas from the small bowel. Faulty absorption might result from circulatory disturbances, from damage to the intestinal mucosa, or from decreased bowel tone. Research workers had overlooked the importance of circulatory changes in producing steatorrhoea, but a study of the relationship between gas absorption and vascularity of the bowel would throw new light on the process of absorption.

Absorption of material through the gut wall was a biphasic process of filtration and reabsorption similar to that of renal excretion: it was governed by the relative forces of the hydrostatic pressure in the capillaries and the osmotic pressure of the bowel contents. This mechanical theory of intestinal absorption not only supported the findings of Frazer and other workers but laid emphasis on deficient absorption, as opposed to impaired fat metabolism, as the basic abnormality in the sprue syndrome.

Biochemical Changes and Vitamin Deficiencies

Dr. A. L. FROEHLICH (Antwerp) described some changes in the blood and bile and the vitamin deficiencies resulting from idiopathic steatorrhoea. The few observations on sodium and potassium metabolism suggested that there was a fall in blood sodium and chlorides, the potassium content remaining unchanged. A fall in blood potassium had been noted in one patient when oedema disappeared. The serum calcium fell significantly; the phosphorus, though not so constantly reduced, was between 1.35 and 2.5 mg.% in four patients. The alkaline phosphatase was sometimes raised. Reduction of the serum proteins was caused by a decrease in albumin; the globulin was normal or slightly raised. The blood fats, cholesterol, and phosphates were usually lowered, but neutral fat was normal. Similar changes had been found in patients with malnutrition and with Addisenian anaemia. There was little increase in the blood sugar after ingestion of glucose, but hypoglycaemia sometimes occurred later. This might be caused by delayed absorption, although the late hypoglycaemia suggested that the glucose was deposited in the liver and failed to reach the peripheral blood. Alterations of the blood fat levels after a fatty meal were less definite. Most workers had found that increase in the blood fat was absent or delayed, and Frazer had not found any increase in the chylomicron count. The serum cholesterol was either unaltered or diminished, and the increase in blood phosphates was less than normal. In Dr. Froehlich's experiments there had been no increase in the blood fat after a fatty meal, but hyperphosphatidaemia and hypercholesterolaemia had occurred as in normal subjects. In three patients otherwise showing the typical picture of steatorrhoea bile acids and choline were unaccountably absent from the duodenal fluid. This might have resulted from liver failure, and it was possible that such cases constituted a separate aetiological group. Dr. Froehlich had been unable to confirm the hypothesis that in steatorrhoea there was deficient synthesis of acetylcholine in the intestinal wall.

Vitamin-B deficiency was commoner in tropical sprue than in idiopathic steatorrhoea, but in both disorders hyperchromic anaemia was often found. The anaemia often responded to normal doses of vitamin B_{12} or to folic acid, but in some cases the response was poor. The commonest deficiency was that of the fat-soluble vitamins. The blood levels of vitamin A were usually low, and, although hypoprothrombinaemia was often encountered, it seldom gave rise to bleeding. In one patient a pigment similar to that found in experimental vitamin-E deficiency had been demonstrated. Commonest of all was deficiency of vitamin D, leading to osteoporosis and tetany, with associated low serum calcium and diminution of calcium excretion in the urine.

Aetiology of the Syndrome

Professor A. C. FRAZER (Birmingham) sought to elucidate the many problems in the aetiology of idiopathic steatorrhoea and similar disorders. He considered that it was first necessary to determine the site of the fundamental defect. Although it had been postulated that liver failure and adrenal insufficiency were responsible for this group of diseases it seemed probable that changes in hepatic function were secondary, and that adrenal failure did not play a leading part. It had now been fully established that pancreatic enzymes were produced normally in steatorrhoea. There was, however, ample evidence to show that the small intestine was at fault. Fat-balance tests and the absence of an increase in blood fat after a fatty meal clearly pointed to deficient absorption; but defective absorption was by no means confined to fat, since it was readily demonstrable that glucose and urea, when given by duodenal intubation, were similarly affected. Insufficient absorption arose from mechanical rather than chemical causes. Radiographical studies shed considerable light on the causation of steatorrhoea. The "clumping" pattern so characteristic of steatorrhoea could be reproduced in normal subjects by giving substances such as fatty acids which stimulated mucus secretion in the small gut. The effects of these mucogenic stimuli had been reproduced in the laboratory and in isolated intestinal loops. If a non-flocculable barium sulphate suspension was used instead of a simple barium sulphate suspension in patients with steatorrhoea, "clumping" did not occur, but it was nevertheless evident that the small gut was both dilated and immobile. A third approach to the problem was through the knowledge that children with coeliac disease improved when wheat flour was withheld

from their diet. It had been shown that wheat gluten rather than wheat starch was the important factor. Wheat gluten did not exert its adverse influence through an allergic response, since other manifestations of allergy were absent. Professor Frazer concluded by postulating that the sprue syndrome was initiated by certain alimentary factors, such as infection, infestation, or the ingestion of rancid fats, which gave rise to increased mucus secretion and increased bacterial growth in the small bowel. The ensuing delay in absorption and decreased motility encouraged further bacterial changes and created a vicious circle that could best be broken by dietary restriction or control of intestinal flora.

Corticosteroid Therapy

Dr. CHESTER M. JONES (Boston) outlined current views on the sprue syndrome and described the response of this disease to corticosteroid therapy. He preferred to use the term "sprue syndrome" because of its wider implications. Although tropical sprue responded to replacement therapy with liver, folic acid, and vitamin B_{12}, response in non-tropical sprue, when there was an abnormality in the small intestine, was less constant. Nine patients with non-tropical sprue, having failed to improve under standard treatment, had been treated with cortisone or A.C.T.H. Treatment had not been given in the belief that their illness was due to failure of the adrenal cortex, but in the hope that corticosteroids might modify and improve intestinal absorption. All patients had shown striking clinical improvement. After three or four days' treatment abdominal distension had disappeared; within a week or ten days the stools had become less frequent and semi-formed, and the faecal fat had diminished. One patient had initially failed to improve because inadequate dosage had been given. Coincidental with clinical improvement there had been gain in weight, increase in the serum proteins, and correction of anaemia. Objective laboratory tests, such as the glucose and vitamin-A tolerance curves and chylomicron counts, had reverted to normal. Dr. Jones believed that corticosteroids actually stimulated the absorption processes which were deficient in the sprue syndrome.

From the enthusiastic discussion which followed the opening papers it was evident that world-wide interest was being aroused by the many problems of steatorrhoea. Among those who discussed the subject were Dr. F. Bulic (Yugoslavia), Dr. H. A. Salveren (Norway), Dr. A. Vaz Serra (Portugal), Dr. W. T. Cooke (Birmingham), Professor C. Jiménez Diaz (Madrid), Dr. R. H. Girdwood (Edinburgh), Dr. D. Adlersberg (U.S.A.), Professor E. Martin (Switzerland), Dr. C. Holten (Denmark), and Dr. J. L. Castro (Spain). Dr. BULIC described an epidemic form of sprue which had occurred in the Yugoslav Army and which had ceased when fresh supplies of fresh food had become available, Dr. SALVEREN commented on the low blood pressure in patients with steatorrhoea, and Dr. GIRDWOOD discussed the absorption of various anti-megaloblastic factors from the bowel.

II.—FLUID AND ELECTROLYTE BALANCE

On Tuesday, September 16, the day was devoted to a symposium on the clinical importance of disturbances of fluid and electrolyte balance. In the morning the chair was taken by Dr. A. GIGON (Basle) and in the afternoon by Sir HAROLD HIMSWORTH (London).

Professor J. G. G. BORST (Amsterdam) opened the symposium by describing the part played by the kidney in governing fluid balance. He emphasized the importance of recognizing three types of diuresis. The first, water diuresis, took place after drinking water. Absorption of water led to a fall in the electrolyte concentration in the blood and so inhibited the production of antidiuretic hormone by the pituitary. As a result, the kidneys excreted large quantities of urine with a low electrolyte content. The second, saline diuresis, occurred when salt and water were ingested together, producing an increase in plasma volume, a rise in venous pressure, and (in accordance with Starling's law) increased cardiac output. The kidneys responded by passing excess urine rich in salt and with a slight increase in potassium concentration. This type of diuresis was found in many pathological states, including heart failure, where it had been found that, if venous pressure increased to such an extent that cardiac output, instead of continuing to rise, began to fall, there was a corresponding diminution in salt excretion. Such patients were "over the top of the curve" of both cardiac output and salt excretion. The third type of diuresis was the rhythmic diurnal variation found in normal individuals, who passed more urine by day than by night. It was important to allow for this when measuring diuresis in pathological states. The third type of diuresis normally dominated the other two: it was abolished by cortisone therapy and in Cushing's syndrome.

Hormonal Influences

Dr. F. T. G. PRUNTY (London) discussed the effect of the adrenal hormones on fluid and electrolyte metabolism. He thought it better to study water and electrolytes separately. Patients with Addison's disease maintained in normal water balance with desoxycorticosterone (D.C.A.) did not show normal diuresis after drinking water, and excreted excessive urine at night. This was the basis of the Kepler test. The use of D.C.A. in Addison's disease corrected the loss of sodium and chloride in the urine, and ultimately water loss as well. There was probably an increased reabsorption of sodium and chloride by the distal urinary tubules; it was uncertain whether there was a direct effect on tubular absorption of water. The pituitary's tendency to correct water loss was prevented by the serum hypotonicity in Addison's disease. Cortisone could restore normal water diuresis in these patients by directly altering tubular reabsorption.

The effects of A.C.T.H. on sodium and chloride excretion were well known, but the reasons for the extreme variability in sodium retention were not. Excess sodium excretion sometimes occurred during A.C.T.H. treatment, but more often after withdrawal of the hormone. This effect was not due to adrenal cortical insufficiency nor to contamination of A.C.T.H. with posterior pituitary. The conflicting results from giving D.C.A. and cortisone to patients with Addison's disease suggested that there might exist an adrenal hormone concerned directly with electrolyte metabolism. In A.C.T.H. therapy oedema could arise without obvious fluid retention, suggesting there was transference of fluid from the cells to the extracellular fluid. Further studies on these problems were in progress.

Renal Failure

Professor ROBERT PLATT (Manchester) spoke of the control of water and electrolytes in renal failure. The primary cause of renal failure was a diminution in the number of functioning nephrons. Animals surgically deprived of most of their kidney substance had excretory disturbances like patients with renal failure. Even in advanced renal failure the daily excretion of urea, creatinine, and electrolytes remained normal. Water excretion and fluid intake were increased. Both in patients and experimental animals there was glomerular and tubular enlargement: it had been estimated that the glomeruli could filter at one and a half times their normal rate. It was clear that, if water and electrolyte excretion was maintained after the glomerular filtration rate had been reduced to one-fifth, each tubule must excrete five times as much fluid as before. This was largely due to decreased reabsorption. The high rate of excretion could be maintained only by a state of permanent osmotic diuresis where the solute load determined the urinary volume and concentration. Many of the features of water diuresis in the failing kidney were more easily explained if it was assumed that the tubules could excrete a hypotonic fluid.

Other evidence for tubular excretion was the knowledge that certain substances were secreted by the tubules in health and disease, and that hypotonic urine was secreted by the tubules of certain aglomerular fish. From the clinical viewpoint it was important to remember that patients with renal failure needed plenty of water and salt: protein restriction reduced the blood urea and so lessened osmotic diuresis.

Diabetic Coma

Dr. RENÉ S. MACH (Geneva) outlined the changes in fluid and electrolyte balance in diabetic coma. During diabetic acidosis patients became severely ill from excessive loss of electrolyte and fluid from the kidney. Estimates of the magnitude of these losses had been made in diabetic patients who had ceased to take insulin and during the treatment of diabetic coma. Sodium was lost partly as sodium chloride and partly in combination with ketones. The sodium was derived mainly from extracellular fluid. It was not known if any diminution of intracellular sodium took place. Diabetic patients lost potassium derived entirely from the cells, and retained potassium when insulin was given. Water was lost not only in the urine but also from hyperventilation and vomiting. If the patients were given water but insufficient salt, hypochloraemia resulted; the tonicity of extracellular fluid depended on the amounts of salt and water lost by the kidneys compared with the amount ingested. Loss of cellular potassium began immediately acidosis occurred and progressed slowly. The plasma potassium level depended on many factors, of which the acid-base balance, insulin and glucose therapy, and saline administration were of practical importance. The losses of salt and water were produced in several ways. Hyperglycaemia produced osmotic diuresis, and water loss was accentuated by anorexia, vomiting, and hyperventilation. Acidosis caused sodium and potassium loss because inorganic base was removed with ketones, and because acidosis favoured cation excretion.

Malnutrition

Professor R. A. MCCANCE (Cambridge) described the conclusions which he and Dr. E. M. WIDDOWSON (Cambridge) had drawn from their investigations on the body changes in malnutrition. Recent technical advances had made it possible to study in detail the changes in body fluids and in the various organs. The hallmark of malnutrition was not a fall in body weight or even diminution of body fat. The really important change was a big increase in the extracellular fluid together with a fall in the total cell mass. The increase in extracellular fluid was brought about largely because fluid replaced the body space which had previously been occupied by fat and cells; additional factors were a fall in the serum proteins and a high salt intake. There was no proof that the changes were produced by renal or endocrine disorders or by vitamin deficiency. Visible oedema was variable and bore no relation to the vast increase in extracellular fluid. The liver wasted in starvation, and it had been possible to show that there was a decrease in individual cell mass due to loss of water and protein. In conclusion, starvation produced no gross changes in electrolyte balance or in cellular structure—a happy coincidence which probably explained the survival of the human race through periods of famine.

Cellular Hyperhydration and Other Topics

Professor J. HAMBURGER (Paris) offered some stimulating thoughts on cellular hyperhydration. Although the clinical signs arising from disturbances of the extracellular fluid were recognized, disorders of cellular fluid were not so well defined. Cellular hyperhydration could be produced either by reducing the osmotic pressure of the extracellular fluid (by infusion of water or removal of salt by dialysis) or by chemical agents such as potassium cyanide or histamine.

Cellular hyperhydration produced gastro-intestinal symptoms, asthenia, headaches, cramps, and nervous symptoms. There were changes in the electroencephalogram, oliguria, and nitrogen retention. The clinical diagnosis could be confirmed by laboratory tests. Cellular hyperhydration could be caused by loss of salt from the body, Addison's disease, shock, or renal diseases with oliguria. Cellular hyperhydration could occur at the same time as extracellular dehydration or generalized hyperhydration with oedema. It was possible that some of the symptoms previously attributed to extracellular dehydration might, in fact, arise from cellular hyperhydration. Care was needed in selecting correct treatment, since the imprudent infusion of hypotonic solutions would aggravate the condition.

Dr. O. J. BROCH (Oslo) spoke on the significance of sodium loss and the role of the serum proteins in regulating osmotic pressure. Some patients suffered loss of total bases from the serum whilst the chloride and bicarbonate remained normal, an apparent acid surplus resulting. Possibly there was a corresponding reduction of the base equivalent of the serum proteins, which might sometimes behave as bases. Serum proteins could therefore vary their base binding capacity without quantitative alteration. Large fluctuations of sodium occurred in the extracellular fluid, but unless there was also an upset of water equilibrium they gave rise to no ill effects.

Effect of Surgery

Mr. A. W. WILKINSON (Edinburgh) described the disturbances in body fluids in surgical patients. The metabolic changes which followed surgical operations reflected local disturbances at the site of injury. They were part of the body's response to injury and could not be modified easily. Unless there was rapid loss of body fluids, infusions of fluid were not required. Starvation and loss of gastric juice in pyloric stenosis presented difficult problems. Duodenal, biliary, and pancreatic fistulae led to loss of intestinal secretions and were a constant drain on the body fluid and electrolytes. All efforts should aim at minimizing the discharges, and if necessary they should be replaced through a jejunostomy. Drowsiness and apathy were the salient features of potassium deficiency; the cardiographic changes did not correspond closely to either the clinical state or the level of serum potassium. Alteration of the acid-base balance of blood was of only secondary importance to changes in sodium and potassium metabolism.

In the discussion which followed the opening papers Dr. D. A. K. BLACK (Manchester) described the changes in pure potassium deficiency induced by taking exchange resins together with extra sodium. Potassium deficiency was associated with sodium retention and increase in the volume of extracellular fluid. Potassium deficiency could be partly compensated by alkalosis, but when it was accompanied by acidosis, as in diabetic coma, symptoms were severe. Here, treatment of the acidosis by lactate might spare the necessity of giving intravenous potassium. The following members also spoke: Dr. G. Sala (Italy), Dr. E. Coelho (Lisbon), Dr. E. Azerad (France), Dr. L. Wislicki (Israel), Dr. A. Svanborg (Stockholm), Dr. M. Soriano Jimenez (Madrid), Dr. A. Cajdos (France), and Professor Ask-Upmark (Sweden).

III.—NEUROTROPIC VIRUS DISEASE

On Wednesday morning, September 17, the subject of the symposium was "Some aspects of neurotropic virus disease." Sir RUSSELL BRAIN was in the chair.

Dr. J. R. PAUL (Yale) opened the discussion with a review of poliomyelitis and the virus encephalitides. He emphasized that countries with a high standard of sanitation had experienced high rates of poliomyelitis during the last generation, while in countries with more primitive sanitation poliomyelitis had remained a largely endemic disease occurring particularly in infants, as it was in the nineteenth century. He thought it probable that in these more primitive countries the children gained immunity which protected them against the disease when they became older, while this was not happening in the countries with a higher standard of sanitation; here the disease was tending to occur in epidemic

form and often in adults. Although the virus had been found in sewage, flies, and food, the exact importance of these extrahuman agents in the spread of the disease was still uncertain: they were certainly not essential links in the chain. The most important source of transmission seemed to be man, during the early or late stages of clinical or subclinical infection.

Attempts to eliminate the virus in a community by quarantine measures were unlikely to succeed. And the fact that there were at least three strains of poliomyelitis virus made active immunization methods very difficult. However, attempts were being made to produce a concentrated immune serum for inducing passive immunity during an epidemic.

In discussing other forms of virus encephalitis, Dr. Paul emphasized the importance and frequency of mumps as a cause of meningo-encephalitis, even in the absence of parotitis. Antibody titres could be helpful in the diagnosis of this condition. In St. Louis encephalitis, Japanese B encephalitis, and eastern and western equine encephalomyelitides the virus was transmitted by arthropods, and these diseases tended to occur, as does poliomyelitis, in the summer. In many cases there appeared to be a viraemia without evidence of neurological involvement, and he thought that the occasionally severe and spectacular infections in man were only accidents in the general epidemiological picture.

Coxsackie Virus and Poliomyelitis

Dr. HERDIS VON MAGNUS (Copenhagen) discussed the Coxsackie group of viruses. This virus was originally isolated in 1947 in the faeces of two cases of paralytic poliomyelitis and since then had been recovered from patients suffering from various clinical pictures. It had been clearly established that strains of the virus had been the cause of cases of Bornholm disease and herpangina, but its significance in other diseases was still uncertain. In particular the relation to poliomyelitis was difficult to be sure about, as both Coxsackie virus and poliomyelitis virus had at times been isolated from the same case. At the moment a virus laboratory could help the clinician only in selected cases, as isolation of the virus and serological examination of paired sera were the only reliable methods, and about 15 different serological types of this virus were known to exist.

Dr. W. RITCHIE RUSSELL (Oxford) discussed some outstanding clinical problems of poliomyelitis. There was still much to learn about the clinical aspects of the disease, and segregation of cases in poliomyelitis centres would assist scientific study. Dr. Ritchie Russell went on to discuss treatment. In patients with pharyngeal palsy, postural drainage was particularly important. He also spoke of the difficulty of deciding what was the best type of respirator to use. There was also division of opinion on the correct treatment of paretic muscles in the early stages of the disease.

Following the major papers, short contributions were made by other speakers, including Dr. O. THORDARSON (Reykjavik), who described an epidemic of myalgia in Iceland thought to be due to a strain of Coxsackie virus. Professor C. H. STUART-HARRIS (Sheffield) described a small epidemic of herpangina in which a Coxsackie virus had been obtained from the faeces of one of the patients.

IV.—ANTIBIOTICS

In the afternoon of Wednesday, September 17, with Sir LIONEL WHITBY (Cambridge) in the chair, Sir ALEXANDER FLEMING (London) reviewed the development of antibiotics in medicine. It was striking how penicillin had converted many serious diseases into trivial complaints. Only a few of the antibiotics found by research had come into use, since many were toxic and others ineffective. In clinical use it was necessary to select that antibiotic which was effective against the particular infecting microbe and also to ensure that it reached the microbe (and not only the blood stream) in therapeutic concentration. Combinations of antibiotics had to be chosen with care. Jawetz had divided antibiotics into two groups: group I including penicillin, streptomycin, and bacitracin, and group II chloramphenicol, aureomycin, and terramycin. It was safe and often helpful to combine drugs in group I, but there was no advantage in mixing drugs in group II. The greatest care was needed in combining a drug from group I with one from group II, since if the organism was sensitive to the group I drug there would be antagonism, although if it was insensitive there would be synergism.

Professor F. MAGRASSI (Naples) described the dosage and complications of antibiotic treatment. There had been some change in the behaviour of antibiotics since the early days when their clinical effect had paralleled the laboratory findings; nowadays this was not always true. A number of biological factors were probably concerned with the action of antibiotics in the body. The direct toxic effects of antibiotics varied enormously; penicillin was quite safe, whereas streptomycin, and to a less extent aureomycin and chloramphenicol, could be dangerous. Complications could also arise from allergy and from rapid destruction of bacteria. The extent to which antibiotics interfered with the development of natural immunity was uncertain. Secondary effects of antibiotic therapy arose from the development of resistant organisms and from suppression of normal intestinal bacteria which were useful to the body.

Behaviour in the Body

Professor A. KEKWICK (London) outlined the behaviour in the human body of the five commonly used antibiotics. After absorption streptomycin, aureomycin, and terramycin were rapidly distributed throughout the extracellular fluid, but penicillin and chloramphenicol were more widely distributed and were poorly concentrated in certain tissues. Behaviour of antibiotics at the blood–brain barrier varied; penicillin and terramycin concentrated poorly in the cerebrospinal fluid, but chloramphenicol diffused rapidly. The concentration of antibiotics in tissues and body fluids was described in detail. All antibiotics were excreted by the kidneys, but, whereas penicillin and terramycin were predominantly disposed of in this way, chloramphenicol and aureomycin were to a large extent broken down by the body. Absorption of penicillin from the intestine was very irregular and there was practically no absorption from the skin. It was possible to forecast the behaviour of the common antibiotics after administration in their usual doses.

Professor C. JIMÉNEZ DIAZ (Madrid) deprecated the indiscriminate use of antibiotics because of the harmful results which might accrue and described the uses of antibiotics in certain diseases. He emphasized the increasing number of strains of resistant organisms and the occurrence of "crossed resistance" between aureomycin and terramycin or chloramphenicol. Antibiotics might have useful therapeutic effects apart from their use in infections. Aureomycin could prevent the development of some experimental anaemias, and had some effect on hepatic cells, since it had benefited patients with hepatitis and cirrhosis. Aureomycin was also of value in post-irradiation sickness.

Much stimulating discussion followed the opening papers, but space does not permit it being described in detail. Dr. NANNA SVARTZ (Stockholm) described electron microscopic studies on the effects of antibiotics on bacteria. Professor C. D. DE LANGEN (Utrecht) considered possible means of reducing the barrier between the blood stream and the infection processes. Dr. B. OLHAGEN (Sweden) drew attention to the appearance of acid-fast organisms other than tubercle bacilli in the sputum of patients treated with antibiotics. Other speakers were Dr. K. G. Bengtsson (Sweden), Dr. E. Nyman (Sweden), Dr. J. Andreu-Urra (Spain), Dr. F. van Goidsenhoven (Belgium), Dr. V. Gorlitzer von Mundy (Austria), Dr. Najib Farah (Egypt), Dr. F. di Raimondo (Spain), Dr. L. V. Schneider (U.S.A.), Dr. M. Janbon (France), and Dr. F. Musotto (Italy).

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Haematological Applications of A.C.T.H. and Cortisone

SIR,—While I have no clinical contribution to offer in the controversy concerning the haematological applications of A.C.T.H. and cortisone, some of the experimental findings of my colleagues and myself in studies of animal bone marrow may be relevant. Our work started in 1944[1] when, in an attempt to solve the mystery of the large numbers of lymphocytes daily leaving the blood, we began to apply quantitative methods to the study of the cell content of bone marrow. We used the costal marrow of the rabbit. The technique was unsatisfactory in several respects, but, taking all these into consideration, we concluded at that time that the number of lymphocytes normally present in the bone marrow was of the same order as the number daily leaving the blood.

In the meantime, Dougherty and White[2] had reported that A.C.T.H. and 11-oxysteroids exerted a lymphoclasic action. Though unable to confirm their results in either blood or lymphoid tissue,[3] and though with cortical extract in the dosage employed we actually induced a lymphoid tissue hyperplasia, we nevertheless felt that without accurate knowledge of the bone marrow it was difficult to assess changes in the circulating blood, such as eosinopenia or lymphopenia. Accordingly, after numerous trials, we found that the bone marrow of the guinea-pig humerus lent itself much more effectively to quantitative study, and we proceeded to investigate the effects of single doses of A.C.T.H. and cortical extract ("eschatin," Parke, Davis & Co.) on the bone marrow.[4] We found no marked change in the marrow eosinophils, but, somewhat to our surprise, a significant increase in the marrow lymphocytes instead of the anticipated decrease. This seemed worth following up, and accordingly we treated a further batch of guinea-pigs with daily injections of A.C.T.H. for 7 days.[5] This time, though there was a slight increase in the lymphocytes and no definite change in the eosinophils, there became evident an increase in both the myeloid (neutrophil) and erythroid cells of the marrow.

However, one injection of A.C.T.H. daily did not seem to be the best way of giving this substance. Furthermore, it was thought that more precise information might be obtained by using individual steroid compounds. Accordingly, together with Drs. Ancill, Holt, and Owen Smith, we gave daily injections of cortisone (5 mg. per injection) for 7 days to 30 young male guinea-pigs. A detailed account of these experiments is at present being prepared for publication, but in view of the correspondence in your columns a brief summary of the results may be of interest to your readers.

As compared with 30 control animals—and despite what our endocrinological colleagues told us about the relative refractoriness of the guinea-pig to cortisone—there is a statistically significant increase in the absolute count of the nucleated cells of the bone marrow, so appreciable that it is reflected in an increase of the specific gravity also. The change affects both the myeloid (neutrophil) and erythroid cells, but more especially the latter, to such an extent that one is tempted, even apart from the present controversy, to speculate on a possible function of steroid compounds as erythropoietic stimuli.

Ten experiments with hydrocortisone (free alcohol) gave similar results. Seven experiments with compound A appear to give evidence of increased transformation of reticulum cells to granulocytes, with what may be a short-circuiting of the typical myeloblast stage. However, neither the eosinophils nor the lymphocytes of the bone marrow underwent any striking changes, and the mystery of the latter remains as elusive as ever.—I am, etc.,

Bristol. J. M. YOFFEY.

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4 —— Metcalf, W. K., Herdan, G., and Nairn, V. (1951). *British Medical Journal*, **1**, 660.
5 Hudson, G., Herdan, G., and Yoffey, J. M. (1952). Ibid., **1**, 999.

The Perennial Peptic Ulcer Palaver

SIR,—May I express my pleasure in reading Sir Robert Hutchison's grand remonstrance on peptic ulceration (August 30, p. 513)? It is an honour to have one's breeches taken down by such a master of the art. I have received verbal chastisement at the same hands before, but never so pleasantly phrased.

In framing my reply, my chief difficulty is that I agree with everything that Sir Robert wishes to say to me. I always seek surgical advice for patients with chronic ulcers, both before and after haemorrhage, though my confidence in this course has been slightly shaken by a sideways glance at that part of the letter addressed to the surgical Ogilvie (in the light of whose reputation the lesser Ogilvies shine with reflected glory).

In conclusion may I, through you, Sir, tell Sir Robert of the keen pleasure which it has given to his many friends in Newcastle to read a letter from him composed in the old authentic style. We can almost hear him saying, "Hoots, toots," once more.—I am, etc.,

Newcastle-upon-Tyne. A. G. OGILVIE.

SIR,—I am without an answer to Sir Robert Hutchison's gentle banter (August 30, p. 513), except to particularize Arthur Hurst's remark by saying that the worst thing that happened to gastric surgery was the remarkable success of a usually unsuccessful operation in the case of the President of the Royal College of Physicians.

Dr. H. Maitland Moir (p. 514) is not alone in regarding the stomach purely as a producer of acid. Meulengracht and others have shown that the cardiac glands and the glands of the pars pylorica secrete an alkaline fluid rich in mucus, and more recently J. N. Hunt has studied the alkaline factor in gastric secretion: in the summary of a recent paper[1] he says: "A reduction in the concentration of acid in the gastric contents does not necessarily mean a reduction in the amount of acid secreted. Duodenal regurgitation is of only minor importance in neutralizing the acidity of the gastric contents. Most of the alkali is secreted by the stomach."—I am, etc.,

London, N.W.8. HENEAGE OGILVIE.

REFERENCE

1 *Guy's Hosp. Rep.*, 1949, **98**, 185.

A Gastric Gossip

SIR,—Mr. Peter Konstam, having added (September 13, p. 614) some interesting facts from West Africa to the discussion of Sir Arthur Porritt's gastric gossip, emboldens me to produce a few from East Africa. There we find a considerable variation in the diseases amongst the tribes for very similar reasons to those quoted for West Africa by Mr. Konstam. In Uganda, with which I am most familiar, besides the tribes of the territory we have a considerable number of immigrants from the Belgian Congo.

Up to recent years the incidence of peptic ulcer in Uganda appeared to be very small. In a review of 1,020 necropsies done at the Kampala Government hospital prior to 1949 evidence of gastric ulceration was found in only 3 cases. These figures are not easy to understand, as my colleagues just over the border in the Belgian Congo have been operating on peptic ulcer patients for more than 10 years.

In June this year, in Uganda, I reviewed patients treated by us in the previous four years at Mengo Hospital, Kampala, and out of a total of approximately 10,000 in-patients

(medical and surgical) treated in that time there were 41 cases of proved peptic ulceration and 7 of carcinoma of the stomach, most of these latter arising in an ulcer. It is true that these are few, but this year the numbers admitted for peptic ulceration have increased markedly. The type of patient in whom it occurs is still the same, mostly of the peasant class, though more of the "chief" class and clerks are being seen. I am not sure yet whether the incidence is rising, or whether successful treatment encourages others to come.

Most of the ulcer patients come from tribes who make a habit of indulging in one vast meal at the end of the day, and take practically no food the rest of the day. A good many of them are steady pipe-smokers and many are of the highly strung type. The 48 cases are too few to be significant, but they are proved cases of peptic ulceration and carcinoma of the stomach. It is said that 10% of the British population suffer from peptic ulcer, but in East Africa it would be difficult as yet to assess the figure. The numbers passing through our hands so far do not suggest anything approaching this high figure, but we have not got a practitioner in every village. However, it was interesting to find that even in this very short series the ratios of duodenal ulcer to gastric ulcer, and the sex incidence, are almost identical with the average of the United Kingdom.—I am, etc.,

Kampala, Uganda. C. J. S. SERGEL.

Cardiac Arrest During Operation

SIR,—The authors of "Acute Circulatory Failure During Surgical Operations" (September 6, p. 533) rightly emphasize the difference between cardiac arrest due to anaesthetic hazards, such as asphyxia and chloroform poisoning, and heart failure due to surgical hazards such as blood loss and traumatic shock. The cardinal feature of the latter group is lack of venous return to the heart, and the futility of treatment by cardiac massage is brought home to the surgeon who palpates the heart in these cases. The heart is a flabby empty bag which is in urgent need of blood both to stimulate it to beat and to nourish it. Alexander and Hewer in their medical memorandum on "A Treatment of Cardiac Arrest" (September 6, p. 546) touch on the vital factor—namely, the need of the heart for a volume of fluid—and suggest the intraventricular injection of saline as a first line of treatment. A recent experience suggested another way of rapidly restoring the circulating blood volume. Esmarch's rubber bandages are rapidly applied in tight overlapping spiral turns from the toes to the groins of both lower limbs. In this way a considerable volume of blood and lymph is transferred in a very short time to where it is urgently needed.

Case History.—Mrs. C. B., aged 74, admitted with fracture of the neck of the femur. A Smith-Petersen nail was inserted under a low spinal analgesic. During the later stages of the operation she became restless, with sighing respirations, and, while the nail was being driven home, the anaesthetist reported cardiac arrest. Artificial respiration with oxygen and intracardiac injection were tried unsuccessfully. Cardiac massage was resorted to, and two fingers were inserted through an opening in the diaphrgam. The heart was felt to be empty and lifeless and did not respond to massage. As a last resort Esmarch's bandages were wound tightly from toes to groins and then further tightened to occlude all circulation in the lower limbs. Almost at once the heart began to beat strongly. After a rapid infusion of fluid into an arm the bandage tourniquets were removed at intervals and the patient returned to the ward. The pulse remained good until the patient died in cerebral coma 12 hours later.

No originality is claimed for this modification of an ancient method of treating shock, but I do not know if it has been tried before in cardiac arrest under anaesthesia. I am sure this patient would have survived if I had tried exsanguination of the limbs first instead of fussing about with injections. It is not my intention to advocate a trial of this treatment in all cases, but only where there is reason to believe that there is a failure of venous return. Even in these cases there should be no delay in preparing for cardiac massage.—I am, etc.,

Winford, nr. Bristol. A. W. FOWLER.

Sensitivity to Streptomycin and P.A.S.

SIR,—Surgeon-Lieutenant D. G. Julian (August 30, p. 476) described a case, claimed to be the first reported, of simultaneously acquired sensitivity to streptomycin and to sodium P.A.S. in a patient suffering from pulmonary tuberculosis. The following is a report of a case of simultaneously acquired sensitivity to streptomycin and to P.A.S. in a patient suffering from renal tuberculosis.

A man aged 34 years, suffering from unilateral renal tuberculosis, was admitted to hospital in May, 1952. Prior to a nephrectomy, a preliminary course of streptomycin, 1 g. daily, and P.A.S., 20 g. daily in four doses, was commenced on July 15, 1952.

On August 15 he developed symptoms of shivering, headache, and generalized aching, suggestive of impending influenza, although the temperature remained within normal limits. On August 19 he developed an erythematous rash on the legs; the temperature averaged 100° F. (37.8° C.) and the pulse rate 120 per minute. By the following day the rash had extended to cover the whole body and was extremely itchy. Chemotherapy was discontinued and "benadryl," 100 mg. twice daily, commenced. By August 22 the symptoms had subsided.

In order to determine to which of the agents he had become sensitive it was decided to withhold the benadryl and use one drug only. The patient was sure that streptomycin had been the cause, and in the absence of a better reason it was decided to try P.A.S. first. Shortly after he had received the second dose an itchy erythema appeared again on the legs and he complained of intense headache. No further P.A.S. was given and benadryl was recommenced. The symptoms had subsided completely by the next day (August 23). Benadryl was continued, and on August 24 P.A.S. was restarted in half-strength doses. After the third dose the erythema and headache returned.

The patient had now changed his mind as to the cause of his symptoms. However, he was a little apprehensive, so on September 8 he was given 1 ml. of sterile water, under the impression that it was streptomycin. On September 9, at 10 a.m., he was given streptomycin 1 g. By 5 p.m. the itchy erythema was again present on the legs and the head ached. On September 10 10% of the total white cell count of 6,400 per c.mm. were eosinophils.

There is no question of accumulation of the drugs in the body due to impaired renal function, as all the subsequent reactions occurred on the first days of the test doses. The blood urea estimations were normal before, during, and subsequent to the sensitivity reactions. It is noteworthy that the patient had not expected a reaction from the first trial of P.A.S. and that his slight apprehension of a trial of streptomycin had been completely allayed after the first day when sterile water had been substituted.

The conclusion is that sensitivity reactions to streptomycin and P.A.S. may be identical and that in this case the occurrence of a state of sensitization to both drugs developed simultaneously.

I wish to express thanks to Mr. W. M. Borthwick for his help and criticism and to Dr. M. A. Foulis, physician-superintendent, Robroyston Hospital, Glasgow, for his permission to publish this case.—I am, etc.,

Millerston, Glasgow, E.1. PETER MACPHERSON.

E.C.T. for Prolonged Stupor

SIR,—Dr. P. H. Mitchell's interesting article (September 6, p. 535) shows the need for further investigation of the causes and treatment of cases of stupor. Some of these cases can be fatal within a short time, and it is not generally realized that early and energetic treatment can often effect an early recovery. It may be beneficial to carry out a preliminary diagnostic test. The intravenous injection of about 0.3 g. of sodium amytal in a 2.5% solution will often enable a patient to speak to the psychiatrist. Sometimes a patient talks quite rationally and asks if the doctor thinks he can cure him, while at other times the patient refers to his delusions and appears to be mentally deteriorated. Twenty per cent. of carbon dioxide in oxygen has also enabled a man who has been stuporous for some months to speak rationally for 20 minutes. Fasting blood sugar should also be estimated to exclude hyperinsulinism.

Professor Lopez Ibor at the World Congress of Psychiatry in Paris, 1950, in summing up the indications for the various

physiological treatments (*Proceedings*, 4, 90), mentions that convulsive therapy offers the sole possibility of saving severe cases and that insulin coma can be very dangerous in severe instances of catatonic stupor. He emphasizes, however, the need for giving E.C.T. either two or three times for the first two days or at least once daily for several days. The following is a fuller account of a case which I published in 1948 (*Proc. roy. Soc. Med.*, 41, 575).

A married woman, aged 51 and menopausal, was first seen on May 13, 1947, with a history that for five months she had become silent and depressed. She had talked about suicide, and razor blades were found secreted in her bed. She had suffered previously from mild rheumatoid arthritis. Her blood pressure had gone up from 165/95 to 190/120. She had been given two electrical treatments by another doctor and seemed a little better after each one of them. She was, however, sent to a dietetic home for some weeks and there developed delusions.

On examination the patient was very silent and in a state of terror. She whispered that she heard voices of people who were threatening her. When seen some hours later she was in a state of stupor and waxy flexibility, in which she remained. Next day she made a determined attempt, in a state of catatonic excitement, to throw herself from a window in response to voices. The patient then became quite inaccessible. She had 23 treatments with electronarcosis, 12 of which were on successive days. At the end of that time the patient had gradually become more accessible. Her attitude when she came out of the stupor was that she desired to discuss certain intimate problems relating to her emotional life which she believed were connected with the onset of her illness. The patient experienced great relief. She made a complete recovery and has been in perfect health ever since.

The interest of this case lies in the combination of the endocrine and psychogenic factors in its causation and also the combination of depressive and schizophrenic symptoms. The patient made little progress until the treatment was given every day. She states that she has had no memory disturbance since the treatment. This shows the advantage of using low-tension cerebral treatment which can be given every day without subsequent ill effect. It is easier for the patient if thiopentone and a curare-like drug are given before each treatment. If such therapy is given, a high proportion of stupors will clear up within a matter of weeks instead of years as in the case reported.—I am, etc.,

London, W.1. A. SPENCER PATERSON.

An Unusual Case

SIR,—The following case appears to me to be sufficiently remarkable to be recorded. On May 5, 1952, I was called to see a lady aged 73 years. She had a typical attack of hay-fever—nasal, pharyngeal, and upper respiratory. Antihistamine tablets were prescribed and gave prompt relief. She was a hay-fever subject, and was advised to take the tablets, up to one or two daily, when symptoms occurred. She was seen at three or four daily intervals until May 22, when she appeared to have a mild attack of influenza. After three days in bed she got up and was allowed out on May 28. On June 1 she had a rigor with a temperature of 102.6° F. (39.2° C.). She was given a penicillin injection on three consecutive days, by which time the temperature became normal. After about one week she was better, but kept upstairs for another week, after which she gradually got about and began to go out.

The symptoms of this attack were as follows: It commenced with an attack of yawning, soon followed by malaise, with pain and tenderness across the back of the shoulders and extending less severely down the spinal area to the sacrum, where it was more severe again; then the rigor came on, lasting for nearly an hour and with rapid rise of temperature; this was soon followed by nausea and vomiting. On examination the only physical signs were tenderness across the shoulders and along the costal margin, especially on the right side. Heart, lungs, urine, etc., were all normal. The symptoms subsided in about three days except the nausea, which persisted for over a week. A tentative diagnosis of cholecystitis was made. By June 19 the patient seemed well.

On June 27 another rigor occurred. Penicillin was given as before, and the temperature became normal in three days. The course of this attack was similar to the first, but, feeling puzzled, I called in a physician, who agreed with the tentative diagnosis of cholecystitis. On July 7, before an *x*-ray examination had been arranged, a third attack of rigor and illness exactly repeating the others occurred. No penicillin was given, and the attack pursued the same course as the others. On July 9 she was admitted to hospital, where she remained until July 28, during which time there were no signs or symptoms and all *x*-ray examinations and blood and urine tests were normal. She was discharged home as fit and she seemed well. On July 30 I saw her at 5 p.m. and she seemed quite well, but at 3 a.m. on July 31 she had another rigor and attack just like the former ones. On August 1 a pathological investigation showed the blood to be within normal limits and the urine suggested a possible pyelitis. On August 4 there was another similar rigor attack.

It occurred to me that on the occasion of each of these rigor attacks she had taken five or six hours previously one of the antihistamine tablets. When seen at 5 p.m. on July 30 she said she seemed well except for a slight running of the nose. During that evening she took one of the tablets and the rigor occurred at 3 a.m. On August 4 she took a tablet at 5 a.m. and had a rigor at 9 a.m. She seemed recovered in a few days and began to get up on August 8. On August 12, at 1 p.m., she seemed well and had no physical signs. In the afternoon she went out for a short walk and returned home to tea, and at 6 p.m. her sister advised her to go to bed and accompanied her upstairs. She sat in a chair and said she felt very tired and was therefore helped on to the bed, where she died in a few seconds.

Her sister is a recently retired ward sister from a London teaching hospital, and she confirmed and recorded the details of the attacks since the patient's return home from hospital. At a post-mortem examination there was marked bloodlessness and extensive ante-mortem thrombosis in the pulmonary arteries, and the lungs were dry. Nothing else abnormal was found except some old compression of the liver causing a thin edge to extend slightly below the costal margin. Special attention was given to gall-bladder, kidneys, adrenals, and inner surface of the colon, all of which were normal. The heart was rather feeble, not enlarged, and showed no valvular or coronary disease.—I am, etc.,

Worthing. W. O. PITT.

The Couvade

SIR,—This ancient custom may not so very long ago have been illustrated in various parts of this country, as that "very knowing, overflowing" practitioner, Mrs. Sairey Gamp, appears to me to have had at least one case of it in her own practice. She speaks of it very circumstantially towards the end of her historic quarrel with that other, but lesser, member of the nursing profession, Mrs. Betsy Prig. "I have know'd that sweetest and best of women," said Mrs. Gamp, shaking her head, and shedding tears, "ever since afore her first, which Mr. Harris who was dreadful timid, went and stopped his ears in an empty dog-kennel, and never took his hands away or come out once till he was showed the baby, wen, bein' took with fits, the doctor collared him and laid him on his back upon the airy stones, and she was told to ease her mind, his *'owls was organs. . . .*"

These last three words in italics (mine) make me think of the couvade. I have had in my own practice a case or two of the morning sickness in husbands and other common enough accompaniments of pregnancy in their wives—but that was so long ago as to give me the feeling of having been an accoucheur at the time of the unforgettable Sairey.—I am, etc.,

London, S.W.3. A. R. EATES.

A Case of Psittacosis

SIR,—In view of the recent article entitled "Psittacosis in a Family," by Drs. B. K. Ellenbogen and C. M. Miller (July 26, p. 189), I felt it would be interesting to put on record an isolated case of psittacosis, which occurred recently in general practice.

The patient, a barman aged 32, was first seen on July 21, when he complained of aching all over, shivering, and sweating, and had a temperature of over 103° F. (39.4° C.). There were no physical signs, and he was treated symptomatically at first. On July 22 blood was taken for agglutinations and smears for malaria parasites, all of which proved

negative. His temperature remained high, and he developed a slight cough and a mild gastro-intestinal upset. On July 25 he was given a short course of chloramphenicol, and appeared completely cured in three days' time.

It was not until I had read the above-mentioned article that the possibility of psittacosis came to my mind, as the patient's father kept a number of racing pigeons, which were roosting outside his bedroom window. A further sample of blood was taken and sent to the department of bacteriology, the London Hospital; the serum from this gave a positive reaction to psittacosis antigen, dilutions up to 1 in 32 showing complete fixation, and at 1 in 64 and 1 in 128 partial fixation. Unfortunately, no serum remained from the original sample taken on the second day of the illness with which to compare this result.

No other member of the household has had any similar illness, and none of the pigeons has shown any sign of disease.—I am, etc.,

Chester. I. J. BRODIE RUSSELL.

Motion Sickness

SIR,—Your recent annotation (September 6, p. 553) may give the impression that the histamine antagonists have little or no part to play in the treatment of motion sickness and that hyoscine is always the drug of choice. I find that promethazine-8-chlorotheophyllinate ("avomine") has a very important place in therapy; indeed, in individual cases it may cure where hyoscine fails. A schoolgirl, aged 13, who invariably was sick in buses or cars, notwithstanding the use of hyoscine, was relieved completely by one tablet of avomine before departure. When she returned from the first day's outing she greeted her house mistress, who had administered the pill, with tears in her eyes, saying that it was the first time in her whole life that she had enjoyed a car ride.

Because avomine in ordinary doses has no side-effects, is long-lasting, and can be continued throughout a voyage I advise its use routinely, and the use of a hyoscine preparation only if nausea is experienced in any degree at all. I have been perhaps fortunate with this system, for I have yet to have a failure.—I am, etc.,

Hove. GUY DAYNES.

Operative Method of Thrombosing Varicose Veins

SIR,—I was most interested in Mr. A. Johnston Abraham's article (August 2, p. 260) on a new operative method of causing thrombosis in varicose veins. Since June, 1950, I have employed the same principle on selected cases, but have used a somewhat different technique. Having exposed the saphenous vein in the groin, I expose it at the ankle and through a small opening here I pass up a ureteric catheter until it can be seen in the vein in the groin. To the lower end of the catheter is tied a length of fine silk. I next open the vein in the groin and pull the catheter through the opening, leaving a length of silk in the vein from ankle to groin. Having tied off the vein with the loose ends of silk, the Trendelenburg operation is completed. I have not carried out any histological investigations on my series, but clinically results have been invariably very good.

In my first two cases I used fine silk, but now I use either "mersilene" 00 or fine nylon. The results are practically as satisfactory as with silk, without the severe post-operative reaction. In one case, following the use of silk, the ankle wound refused to heal until I removed about 4 in. (10 cm.) by pulling on the knot and cutting off as high as I could. This was followed by immediate healing of the wound. I have had no such trouble with mersilene or nylon.

In my first case I started at the ankle and introduced the ureteric catheter before exposing the vein in the groin; by the time I had done so there was considerable clot round the catheter and in the subsequent cases I have exposed the saphenous in the groin as the first step. On two occasions I have been unable to push the catheter up the vein to the groin. I was able to get over the difficulty in one case, as I could palpate the catheter at the knee and was able to expose it through a small incision, withdraw it, and, by reintroducing, complete the operation, using two lengths of thread instead of one. I had to abandon the method in the second case and resort to multiple ligations. I am having an elastic bougie made of a slightly larger gauge than the average catheter and with a globular end which I think will get over this difficulty.—I am, etc.,

Bath. F. D. MURPHY.

Prevention of Rheumatic Fever

SIR,—I wonder if I might call attention to an important article (*U.S. Armed Forces med. J.*, 1951, **2**, 607, abstracted in *Bull. Hyg.*, 1951, **26**, 900) on this subject, which, owing to publication in a relatively unfamiliar journal, may not have received the attention it deserves in this country.

It provides evidence that the majority of cases of rheumatic fever and heart disease arising from throat infections could be prevented. The authors found that in 1,178 United States air force personnel who were admitted to hospital with exudate on the tonsils or pharyngeal wall, and were treated with penicillin, only two definite and three possible cases of rheumatic fever occurred, whereas in a control series of 1,162 who received no specific treatment there were 28 definite and seven possible cases. The dosage of penicillin used was 600,000 units of crystalline procaine penicillin G in oil, given intramuscularly on the first, third, and fourth day.

This type of treatment is now quite often employed in general practice for conditions such as carbuncle, cellulitis, and pneumonia. If it were employed on a large scale in all cases of acute sore throat, it seems highly probable that many of the 10,000 deaths and more which occur in England and Wales each year from rheumatic heart disease might be prevented.—I am, etc.,

Sheffield, 10. JOHN PEMBERTON.

Ichthyosis and Hypnosis

SIR,—Dr. John Freeman's lack of surprise (September 13, p. 615) over the improvement effected in the case of congenital ichthyosis by hypnosis causes me considerable surprise. I had the opportunity of observing the treatment of this case over a period of months, and was not only surprised but astounded by the changes wrought in the patient's skin.

I am not quite clear what Dr. Freeman implies by unhesitatingly classifying congenital ichthyosis as an allergic disorder. Does he use the term within von Pirquet's original meaning of an altered or changed reactivity, or in some wider sense? The allergic basis postulated by Dr. Freeman is an interesting speculation, but throws no more light on the aetiology of ichthyosis congenita than on any other of the multitudinous conditions now loosely called "allergic." As Dr. David Harley writes in *Modern Practice of Dermatology*: "It seems likely that the term allergy would itself have been dropped long since had it not been for the strong general feeling that a word so beautiful must mean something. The term allergy has been invested with such an all-embracing meaning that the word itself conveys but little, or rather its vastness prevents any attempt at a precise definition."

As a dermatologist, ignorant of the aetiology, sometimes faced with this distressing disorder, and with no means of treating it, I should be glad to learn if Dr. Freeman as an allergist has discovered any means of relieving this crippling condition.—I am, etc.,

London, S.W.1. K. H. COHEN.

Danger from Cuffed Endotracheal Tubes

SIR,—May I be allowed to reply very briefly to those whose most interesting letters on this subject have followed mine? I was very far from venturing to advise anyone on the treatment of the asphyxia sometimes occurring in these cases; I was merely recording the evidence given at the inquest which I held.—I am, etc.,

Leatherhead, Surrey. C. F. J. BARON.

An Operation for Femoral Hernia

SIR,—In operations for femoral hernia, one of the problems is how to close or cover the femoral ring in order to prevent the possibility of recurrence. This problem is present particularly in cases of strangulated femoral hernia when it has been necessary to divide the lacunar ligament or the inguinal ligament in order to relieve the strangulation. Many ingenious methods have been devised, but I have not seen described the method I have been using during the past two years.

The operation is done with the table tipped so that the patient's head is as low as possible. After cleaning the femoral hernia in the thigh right up to the femoral ring, the inguinal canal is opened by incising the external oblique aponeurosis. The transversalis fascia is then incised and the femoral hernial sac reduced through the femoral ring. In cases of strangulated hernia the lacunar ligament is divided, and, if this is not enough, the inguinal ligament also. The hernial sac is now excised in the usual manner after opening for inspection. With good light and careful retraction the anterior surface of the superior ramus of the pubis is identified. To the outer side is the femoral vein, to the inner side is the pubic spine, and partly covering the ramus is the pectineus muscle or fascia. The upper border of the superior ramus is a definite sharp ridge with abundant periosteum. The pectineus fascia is not sufficiently strong to anchor sutures, but the periosteum of the upper border is.

With a most watchful eye on the femoral vein, a series of tantalum wire sutures (five or six in number) are loosely slung between the periosteum of the upper border of the superior ramus and the posterior surface of the inguinal ligament, from the femoral vein externally to the pubic tubercle internally. A small, strong, fully curved, cutting-edged needle is best for this. There is no tension on the sutures and the idea is to provide a loose filigree. The transversalis fascia is sutured with catgut. A series of loops of tantalum wire (about 12 in number) are inserted loosely to form a filigree between the internal oblique muscle and the posterior edge of the inguinal ligament, to prevent the formation of a direct inguinal hernia later. The external oblique is sutured with catgut.

The chief difficulty in this operation is the common one of adiposity, but with adequate retraction and a good light this can be overcome. The results are excellent.—I am, etc.,

Rotherham. ERIC COLDREY.

Admission of Poliomyelitis Cases to General Hospitals

SIR,—I had not intended to say anything further on this subject, but "Your Expert" in his reply (September 13, p. 617) poses certain questions and invites an answer. I agree that no hospital should knowingly admit cases for which it cannot provide proper and safe treatment. This, surely, is a principle which should be observed in all hospitals and in respect of all diseases. It includes ensuring against exposure to infection. As poliomyelitis provides instances of case-to-case infection and of otherwise associated cases, I fail to see how the risk of cross-infection can be regarded as purely theoretical. That the risk is small, owing, it would seem, to widespread immunity, is scarcely an adequate justification for taking it in a disease of such serious consequence and for which we have no really curative treatment.

I remain, therefore, of the opinion that poliomyelitis patients should only be admitted to wards which are constructed and organized for the isolation of infection and which will have, not only the requisite equipment, but also medical and nursing staff with continuous experience in the treatment of poliomyelitis patients in the acute stage. It is, of course, impossible to speak for every area in the country, but I imagine that in the great majority of areas such wards are to be found in fever hospitals rather than in general hospitals. I agree, however, that a hospital should have regard to the adequacy of its nursing staff in considering the number of cases it can admit.—I am, etc.,

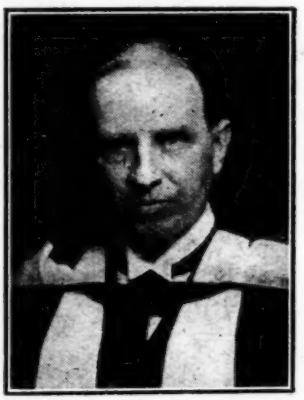
Croydon. J. J. LINEHAN.

Obituary

A. F. TREDGOLD, M.D., F.R.C.P.

Dr. A. F. Tredgold, consulting physician to University College Hospital and an authority on mental deficiency with an international reputation, died at his home in Guildford on September 17, aged 81.

Alfred Frank Tredgold was born on November 5, 1870. His ancestors belonged to the Cornish family of Tregol (or Tragol), but his own branch of the family came from Lincolnshire. Six of his near relatives were also members of the medical profession. Tredgold studied medicine at Durham University and the London Hospital, where he gained several scholarships and prizes. After qualifying in 1899 he was immediately offered a research scholarship in insanity and mental diseases which had recently been founded by the London County Council. He accepted this and chose as his subject mental deficiency, which up to that time had received little scientific attention in England. For two years thereafter he worked in the asylums of the L.C.C. and in the newly built central laboratory at Claybury, then under the direction of F. W. Mott. Working alongside him in the laboratory at that time were Henry Head and Joseph Shaw Bolton. When the scholarship expired Tredgold was faced with the necessity to earn his living and he went into general practice, where he had the opportunity to continue his clinical inquiries into mental diseases, though he had to give up his pathological investigations. In 1905 he was appointed a medical investigator to the Royal Commission on the Feeble-minded, and the experience he gained in this appointment together with his previous research work enabled him in 1908 to bring out the first edition of his *Textbook on Mental Deficiency*, which was at once accepted as the most authoritative work on the subject.



[*Elliott & Fry, London.*

The Bill which was based on the findings of the Royal Commission became the Mental Deficiency Act of 1913, and Tredgold spent much time speaking in support of it at meetings all over the country. By 1914 he had become a recognized leader of professional opinion on this subject, and he was able to go into consultant practice.

The first world war brought about a great change in his life. For a number of years he had been interested in the volunteer movement, and in fact he had been commissioned as a combatant officer in the 2nd Volunteer Battalion of the Queen's Regiment in 1905. At the outbreak of the war, thinking that his services might be needed in the R.A.M.C., he informed the War Office that he was medically qualified, but the authorities decided that specialists in neurology and mental diseases would not be required by the Army and that he should remain as a combatant. So in 1915 he went to Gallipoli (taking part in the Suvla Bay landing) as adjutant of

his battalion, with the rank of major. After the evacuation of Gallipoli he served on the western frontier of Egypt and in Sinai until he was invalided back to England with severe dysentery and cholecystitis. After he had recovered he took command of a Territorial depot until the end of the war, when he was awarded the Territorial Decoration.

After the war Tredgold returned to consultant work, and was appointed neurologist to the Royal Surrey County Hospital and physician in psychological medicine to University College Hospital and lecturer in the medical school. Before taking up these appointments he had obtained the degree of M.D. at Durham University in 1919 and taken the M.R.C.P. in 1921. He held several other teaching posts, including that of lecturer at the annual course on mental deficiency arranged for school medical officers by the Central Association for the Care of the Mentally Defective. In this and other ways he was able to lead public opinion towards a more enlightened view of what had been for so long an obscure though highly important medical and sociological problem.

Tredgold was elected F.R.C.P. in 1929. He was an ex-president of the Section of Psychiatry of the Royal Society of Medicine, and he gave the Galton Lecture to the Eugenics Society in 1927. Probably the work by which he was most widely known was his *Textbook on Mental Deficiency*, which reached its seventh edition in 1946. It is read in medical schools throughout the world. He was also the author of a *Manual of Psychological Medicine* (first published in 1943).

In 1899 he married Zoë, daughter of F. A. Hanbury, barrister-at-law. They had two daughters and one son, Dr. R. F. Tredgold, who is physician to the department of psychological medicine at University College Hospital. In 1947 Tredgold's life was saddened by the death of his wife, to whom he was devotedly attached. Shortly afterwards he lost the sight of one eye as a result of glaucoma, and the vision in the other gradually worsened. Last year a cerebral vascular lesion finally compelled him to give up work, but he remained mentally active, interested in his garden and in preparing new editions of his two books for the press.

A colleague writes: Dr. Tredgold's work was distinguished, especially for those of us who worked in his specialty, by his clarity of vision and clearness of expression. His *Textbook on Mental Deficiency*, first published in 1908, with its succeeding editions, has remained the standard textbook both here and in other English-speaking countries. With Sherlock, Crichton-Browne, Maier, and others he presented the early picture of mental deficiency in two parts, one with intellectual defect and the other with a congenital defect of the moral sense. These general ideas were incorporated in the Mental Deficiency Acts of 1913 and 1927. Though modern work has succeeded in throwing a new light on the psychological basis of conduct we have as yet only got so far as to change for moral sense a fresh expression of personality, without any clearer idea of how the psychopathic person comes to be what he is. Tredgold's regard for essentials made him the great teacher he was. He had chosen for himself a difficult field, where classification and description were far in advance of cause and treatment. Nevertheless he picked out for his students with unerring accuracy the points at which they could help. Those of us who heard him talk remember well that he stressed the great importance, only recently generally recognized, of the parent and family relationship of the defective. It was said of him that no parent who visited him came away without feeling comforted and happier. He recognized the treatment of mental deficiency as a problem which could often be solved within the family circle, and he taught parents how to do it. In this way he was far ahead of his time. No account of him can be complete without reference to his modesty and his strong sympathy for the cause of mental deficiency. With a number of others he worked for a rational approach to a neglected problem and for a recognition by society of its responsibilities towards those for whom he laboured. We of his generation think well of him.

MILLAIS CULPIN, M.D., F.R.C.S.

Dr. Millais Culpin, formerly professor of medical and industrial psychology in the University of London, died at St. Albans on September 14, at the age of 78. Millais Culpin was born at Ware, Hertfordshire, in 1874, the son of the late Dr. Millice Culpin, of Taringa, Queensland, Australia, and was educated at the Grocers' Company's School and at the London Hospital, where he won the Buxton scholarship in 1897, the junior Letheby prize in 1898, and the senior prize two years later. He qualified M.R.C.S., L.R.C.P. in 1902, and after holding a number of resident posts at the London Hospital he graduated M.B., B.S. in 1905, and took the F.R.C.S. two years later. He then went out to Shanghai to practise in the English settlement there, but at the beginning of the first world war he returned to this country and joined the R.A.M.C., being appointed the surgical member of a board in London for sick and wounded officers. In 1915 he was transferred to the Alexandra Hospital, near Portsmouth, as a surgical specialist. A paper, published in this *Journal* in 1915, which he wrote with the late Dr. E. G. Fearnsides was one of the first reports on the subject of war neuroses. The authors drew attention to the fact that many patients with trench-foot displayed hysterical symptoms. Culpin served in France in 1916 and 1917, and, although mainly occupied with surgical work, he had plenty of opportunity to foster his growing interest in functional disorders. Towards the end of 1917 he gave up surgery at the request of the late Colonel Aldren Turner for work in Army neurological hospitals, where he made a study of shell-shock, D.A.H. (disordered action of the heart), and other forms of neurosis. When he proceeded M.D. in 1919 he wrote his thesis on war neuroses, and in the following year his book, *Psychoneuroses of War and Peace*, was published by the Cambridge University Press.

After the war Culpin was appointed a lecturer in psychoneuroses in the London Hospital Medical College, and he also worked as a neurological specialist to the Ministry of Pensions. From 1923 onwards he took a large share in the research work of the Industrial Health Research Board. In 1930, when he was in consultant practice, he became lecturer in industrial and medical psychology at the London School of Hygiene and Tropical Medicine, and in the following year he was appointed professor in that subject. Many old students of the school will remember the rather intense half-hour they spent alone with Professor Culpin while he sought for neurotic traits in them and then explained the significance of his findings. Needless to say, his help in the solution of personal perplexities was never asked in vain. He relinquished the chair in 1939. In 1944 Culpin was elected president of the British Psychological Society, an honour which greatly pleased him. His special knowledge was of service to the British Medical Association, for he was a member of the Committee on Miners' Nystagmus, of the Psychological Medicine Group Committee, and of the Committee on Mental Health. Among the books he wrote were *Spiritualism and the New*

Psychology (1920), *The Nervous Patient* (1924), *Medicine and the Man* (1927), *Recent Advances in the Study of the Psychoneuroses* (1931), *Mental Abnormality: Facts and Theories* (1948), and, with Dr. May Smith, *The Nervous Temperament*. It is only a short time since a paper which he had entitled "Clinical Psychology and Some Forgotten Episodes" was accepted for publication in this *Journal*.

In 1913 Dr. Culpin married Miss Ethel Maude Bennett, daughter of Mr. E. Dimery Bennett, and she survives him, with the one daughter of the marriage.

Dr. HENRY WILSON writes: Millais Culpin had been a Fellow of the Royal College of Surgeons for forty-five years. It was because his clinical ability was highly valued that his appointment as lecturer on psychoneuroses at the London Hospital was so easy, some years indeed before psychoneuroses were accepted on the curriculum elsewhere. Culpin's progress to such a position and to his professorship at the London School of Hygiene might well be an example for those aspiring to psychiatric eminence. Culpin's interests before 1914 had been largely surgical. It was as a surgeon in the British Expeditionary Force in 1914–18 that he began to detect that many abdominal symptoms were, in fact, associated with psychological upsets, not with diseases which could be verified by the naked eye. He stated his views to horrified seniors, but his clinical dexterity assured his views of a better reception than would have been accorded to those of a less skilful observer or a less tenacious advocate. His knowledge of psychiatry was largely self-taught. He did not in fact work at any of the hospitals for functional disorders with which Rivers, Hart, Hurst, or Crichton-Miller were associated. He read widely, and he applied his knowledge with a fresh mind to "railway spine," miners' nystagmus, and obsessional drives. There was a simplicity about some of Culpin's investigations which might be the model for more recent work. His interests were practical and industrial. He worked for long with the Industrial Health Research Board. He was always something of a lone figure. His rugged countenance mirrored an acerbity of mind which covered a gentleness and humility which many may not have suspected. It was this humanity which attracted to his table at the Royal Society of Medicine many younger men of far other specialist leanings, with whom he exchanged clinical and wider information and to whom he poured out stories of adventure and fortitude from his early Australian days. It was this quality of mind that also kept him young in outlook and made him almost to the last ready to spring into correspondence with those expressing views with which he agreed or disagreed. He had an almost Victorian attitude to justice. He wrote many letters seeking more equitable arrangements for those whom law and tradition had wronged. This passion probably limited his close friendships, yet it was so much a part of the man that none would have wished it different. It gave his writings a twist of originality which did not make them widely read, yet he was a successful therapist owing allegiance to no one school.

Sir RICHARD GREGORY, D.Sc., LL.D., F.R.S.

Sir Richard Gregory, who died at Middleton-on-Sea, Sussex, on September 15, at the age of 88, held for many years a position and status in scientific journalism which during his lifetime was unique, and may well remain so. It was primarily through his work, influence, and practical judgment that *Nature*, founded by Sir Norman Lockyer in 1869, was carried not merely to stability but to recognized pre-eminence as the leading journal of general science published in any language or country. In a world increasingly competitive, the comment, made as a factual statement by a fellow editor, that "there can only be one *Nature*" is the measure of his achievement.

After four years as computor to the solar physics committee and assistant to Sir Norman Lockyer in his astronomical and other work, Gregory was appointed in 1893 as assistant editor of *Nature*, a position which he held with increasing responsibility and stature until 1919, only one year before Sir Norman's death. The twenty years of editorship which followed do him less than justice in strict chronology. His acquaintance among scientific workers was astonishingly complete. More than other editors he had need for quick and critical judgment, since the publication of a letter in *Nature* was the recognized means of preliminary report in a very wide area of science. His personal reputation combined a widespread benevolence and an absolute integrity as its most important ingredients. The key to his position was his real and evident interest, not only in scientific publication for its own sake but in the dissemination of scientific knowledge as a contribution to general education. He believed also in the assertion of the influence of science on general affairs. These attitudes were reflected in leading articles in *Nature* and through the foundation of the British Science Guild, for which he was largely responsible. In the educational field, he had a platform in the *School World* and the *Journal of Education*, of which he was joint editor. He also gave freely of his time and ability to many organizations in which he was interested Academically, he was for a time professor of astronomy at Queen's College, London. But it is primarily as a great editor that he will be remembered, and his election to the Fellowship of the Royal Society under Rule XII was indeed the recognition of "conspicuous service to the cause of science."

Dr. IAN MACKINNON JEFFERISS, who died at Totnes, Devonshire, on September 7, at the age of 73, was born at Kippen, Stirlingshire, on March 31, 1879, the son of Dr. W. R. S. Jefferiss, latterly of Chatham, Kent, and grandson of Dr. R. R. Jefferiss, of Dalkeith, Midlothian. He began his medical studies at the age of 16 at King's College Hospital, London, and qualified M.R.C.S., L.R.C.P. in 1900 at the age of 21. After holding resident posts at his own hospital and elsewhere he entered general practice in 1904 at Kirkoswald in Cumberland. He then moved, in turn, to Gillingham in Kent, Exeter, Okehampton, London, Shebbear in Devonshire, Lakenheath in Suffolk, and finally, in 1927, to Totnes, where he remained in practice until his death. He was a member of the staff of the local hospital for 25 years and was medical officer of health for the borough of Totnes until 1943, when he resigned the post. He was much loved by his patients and held in great respect by his colleagues. In 1906 he married Mary Gordon, daughter of the Rev. C. J. Gordon, of Great Salkeld, Cumberland, and had two sons, who carry on the medical tradition of the family. In 1925 he married Winifred Harvey, having one daughter by her. They both survive him.

Mr. HERBERT GEORGE LETCHER, who died on September 10, aged 49, at his home at Acton, where he had been in general practice for 15 years, was born at Kadina, South Australia, on August 16, 1903. He was educated at St. Peter's College, Adelaide, and later entered the University of Adelaide and the Royal Adelaide Hospital, graduating M.B., B.S. in 1927. Both in college and in his medical school he showed an intellectual prowess far above the ordinary, together with an aptitude for athletics which made him outstanding in cricket, tennis, and swimming. After graduation he assisted his father in his practice in Adelaide for a short time, but the love of the mother country and an urge for surgery brought him to London, where he took

his F.R.C.S. in 1931. Then followed resident surgical appointments at the East Surrey Hospital, Redhill, the Victoria Hospital, Westcliff-on-Sea, the Radium Institute, and the Central Middlesex Hospital.

Mr. T. G. I. JAMES writes: Life in London appealed to Letcher very much, and the example of his father and his love of people led him to a career as a general-practitioner surgeon. With this end in view he settled in Acton in 1937 and became a member of the surgical staff of Acton Hospital, where, during the earlier part of the last war, he showed skill, dexterity, and speed in dealing not only with air-raid casualties but with the large number of general patients whom he was called upon to treat. He was particularly interested in the acute abdomen and in urology, but he was a sound all-round general surgeon. During the last war he served overseas in the R.A.M.C. as a surgical specialist, with the rank of major, mainly in the Middle East and in the Sudan. On his return to civil life, changing circumstances forced him to relinquish his activities as a surgeon and to devote his whole time to general practice, to which he gave his heart, but he still kept in touch with surgery and remained an active Fellow of the Royal Society of Medicine. His personality was unique. A short, dapper figure, always neat and full of vitality, he radiated from his sparkling eyes and round, smiling face a warmth and friendliness which brought him countless friends. Nothing could ever damp his ebullient spirit and the sun always shone wherever he happened to be. One of his characteristics was a chuckle and a laugh that would infect any gathering and dispel any gloom. He lived a full life, and what little time he could spare from his patients he devoted to golf, tennis, racing, and cricket, and in exploring the English countryside with his charming wife and two boys. His home life was most serene, and his was an open house for many friends and a host of Australians, to whom he gave generous hospitality. He was a charming host, full of stimulating conversation, with a wide knowledge of men and affairs. Of few people can it be said that they never uttered an unkind word or performed an unkind deed, but of George Letcher this was true. It will be difficult for his patients, friends, and colleagues to realize his sudden and unexpected death, and all will extend to his widow and children the deepest sympathy.

Medico-Legal

DEATH FROM AIR EMBOLISM

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

A man aged 34 was admitted to the Royal Northern Hospital in June, 1951, suffering from bilateral pulmonary tuberculosis, and underwent a pneumoperitoneum to collapse both lungs. The right phrenic nerve was crushed, leaving him with limited respiratory movement, and his condition was such that after leaving hospital in August, 1951, he had to attend the chest clinic weekly for refills of air to collapse his lungs.

On April 2, 1952, he attended for his refill, and 700 ml. of air was to be injected. The injection was made on the right side because of adhesions on the left, and after 600 ml. had been put in he complained of discomfort, and breathing became difficult. The needle was at once removed, but about 50 ml. more entered during removal. He then got off the table, walked into the passage, collapsed, and died.

At necropsy it was found that the puncture mark of the needle extended into the liver for a total depth of ¾ in. (1.9 cm.). There was a small haematoma at the site of the puncture of the liver capsule, and large bubbles of air were situated underneath. There was a column of air bubbles in the coronary sinuses, and the right side of the heart was filled with a frothy mixture of air and blood.

At the inquest, held at the St. Pancras Coroner's Court on April 7, a verdict was recorded of death by misadventure, caused by air embolism due to injection of air into the hepatic vessels during attempted pneumoperitoneum for double pulmonary tuberculosis.

Universities and Colleges

UNIVERSITY OF LONDON

Inquiries concerning the Wiltshire Memorial Research Scholarship, which is now available for award, should be addressed to the Dean, King's College Hospital Medical School, Denmark Hill, London, S.E.5. The object of the scholarship is to encourage research in cardiology, and the honorarium attached to it is at least £400 a year.

Vital Statistics

Poliomyelitis

Poliomyelitis notifications (uncorrected) in the week ending September 13 (37th week of the year) were as follows: paralytic 115 (115), non-paralytic 68 (73); total 183 (188). This is a decrease of 5 compared with the previous week, the figures for which are in parentheses. Up to and including the week ending September 13 the overall uncorrected notification rate for England and Wales was 6.8 per 100,000.

Paratyphoid in South Wales

Attempts to trace the source of the epidemic of paratyphoid fever which has been smouldering for some weeks past in Monmouthshire and Glamorgan have so far proved fruitless. In Glamorgan alone there have been about 170 cases. Various foodstuffs have been under suspicion, but no incriminatory evidence has yet been found.

Infectious Diseases

In England and Wales during the week ending September 6 a decrease was reported in the number of notifications of measles 712, whooping-cough 30, and acute poliomyelitis 27, while the only rise of any size was 42 for dysentery.

The notifications of scarlet fever were the same as in the preceding week; during the week the incidence fell slightly in the southern section of the country. Although the incidence of whooping-cough declined slightly the largest fluctuations in the local trends were increases of 67 in Lancashire and 49 in London. The number of notifications of diphtheria was 1 more than in the preceding week, and no changes of any size occurred in the local returns. The largest falls in the incidence of measles were London 132, Essex 120, and Lancashire 110.

The number of notifications of paratyphoid fever was 3 less than in the previous week. 15 of the 41 cases were notified in Wales. The largest returns during the week were Middlesex 8 (Edmonton M.B. 4) and Glamorganshire 8.

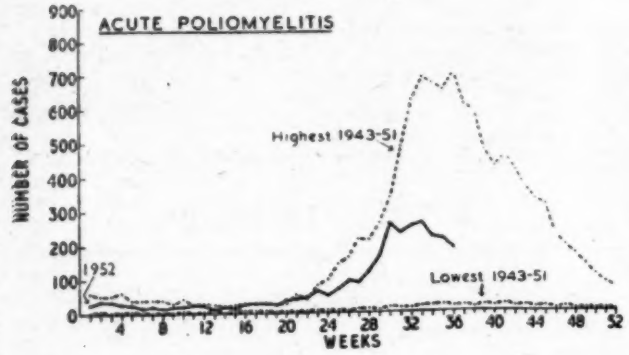
The chief features of the returns for dysentery were a fresh outbreak with 18 notifications in Bristol C.B. and a rise from 9 to 37 in Lancashire. The other large returns were Surrey 18 (Carshalton U.D. 10) and London 17. In Scotland the notifications of dysentery in the outbreak in Glasgow rose to 100.

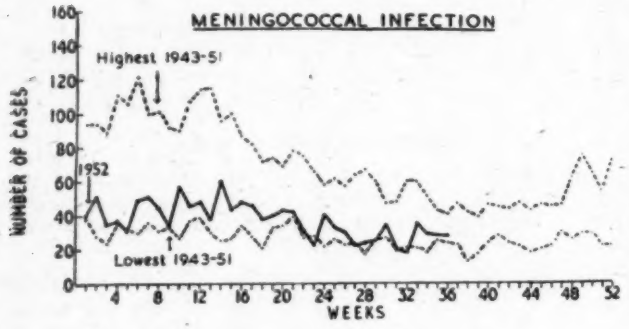
The number of notifications of acute poliomyelitis was 35 less for paralytic and 8 more for non-paralytic cases than in the preceding week. The largest returns were London 28 (Woolwich 6, St. Pancras 5), Essex 23 (Southend-on-Sea C.B. 5, Ilford M.B. 5), Lancashire 13, Kent 10, and Middlesex 10.

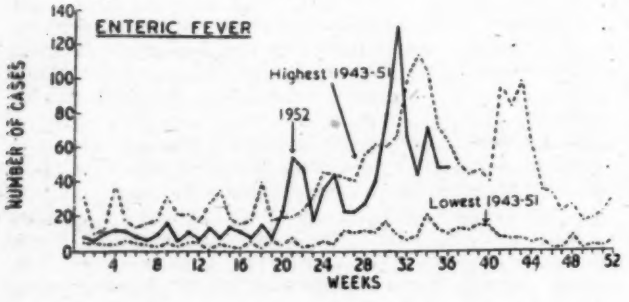
The largest outbreak of food-poisoning notified during the week involved 50 persons in Essex, Tendring R.D.

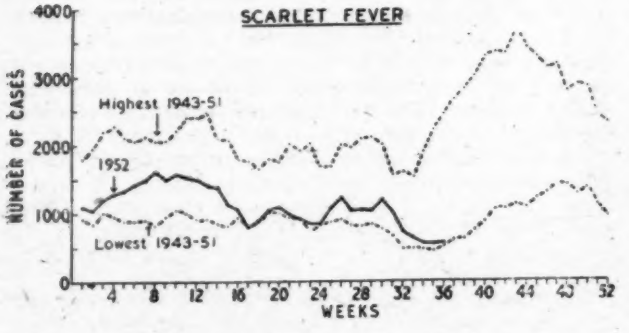
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported during the nine years 1943–51 are shown thus - - - - - - - -, the figures for 1952 thus ————. Except for the curves showing notifications in 1952, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Week Ending September 13

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 701, whooping-cough 1,487, diphtheria 26, measles 2,421, acute poliomyelitis 185, dysentery 100, paratyphoid fever 64, and typhoid fever 9.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **September 6** (No. 36) and corresponding week 1951.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1952 Eng. & Wales	1952 Lond.	1952 Scot.	1952 N. Ire.	1952 Eire	1951 Eng. & Wales	1951 Lond.	1951 Scot.	1951 N. Ire.	1951 Eire
Diphtheria	23	4	8	1	1	40	2	11	3	1
Dysentery	132	17	120	4	4	131	28	76	1	
Encephalitis, acute	5	1	0	0	1	4	0	0	0	
Enteric fever:										
Typhoid	7	0	0	0	1	4	0	0	1	1
Paratyphoid	41	1	1 (B)	1		32	3	4 (B)	5	
Food-poisoning	200	22		1		109	14		0	
Infective enteritis or diarrhoea under 2 years				20	64				14	45
Measles*	2,937	280	38	31	98	1,387	50	71	69	36
Meningococcal infection	28	1	16	0		31	0	10	3	1
Ophthalmia neonatorum	55	3	15	0		27	2	11	0	
Pneumonia†	228	11	162	10		196	15	99	5	
Poliomyelitis, acute:										
Paralytic	115	16	22	9	1	47	2	11	4	1
Non-paralytic	73	12				39	3			
Puerperal fever§	260	36	14	0		231	27	8	0	1
Scarlet fever	557	44	156	11	28	499	28	157	16	15
Tuberculosis:										
Respiratory			121	19				134	35	
Non-respiratory			9	6				19	4	
Whooping-cough	1,831	132	89	54	116	2,576	124	344	56	88

DEATHS in Great Towns	1952 Eng. & Wales	1952 Lond.	1952 Scot.	1952 N. Ire.	1952 Eire	1951 Eng. & Wales	1951 Lond.	1951 Scot.	1951 N. Ire.	1951 Eire
Diphtheria	0	0		0	1	*0*	0	*0*	0	0
Dysentery	0	0		0			0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0		0		*0*	0	*0*	0	
Infective enteritis or diarrhoea under 2 years	6	0	2	1	0	*10*		*0*	2	1
Influenza	4	0		0	1	*5*	3	*2*	0	0
Measles		0		0	0		0	*0*	0	0
Meningococcal infection		0					0	*1*		
Pneumonia	116	15		4	3	*122*	15		8	5
Poliomyelitis, acute	13	1			0	*0*	0			0
Scarlet fever		0		0	0		0	*0*	0	0
Tuberculosis:										
Respiratory	78	9	10	1	8	*98*	12	*17*	4	9
Non-respiratory		1	1	2	1		2	*3*	2	1
Whooping-cough	1	0		0	0	*2*	0	*0*	0	0
Deaths 0–1 year	171	11	20	9	14	*195*	26	*27*	5	23
Deaths (excluding stillbirths)	3,912	549	512	96	138	*3,941*	614	*492*	80	142
LIVE BIRTHS	7,117	1004	811	212	457	*6,753*	1179	**24*	233	423
STILLBIRTHS	179	28	20			*155*	17	*19*		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Refresher Course for General Practitioners.—The 55 refresher course articles published in the *British Medical Journal* between October, 1949, and December, 1950, have been collected together as a book. The book will be ready early next month, and orders should be placed now with the Publishing Manager (B.M.A. House, Tavistock Square, London, W.C.1). The book contains 512 pages, each article has been brought up to date by its author, and there is a full index. Price, including postage, is 25s.

International Congress of Internal Medicine.—By the courtesy of the Right Honourable the Lord Mayor of London the Second International Congress of Internal Medicine held a banquet at the Mansion House on September 17. After the toasts to the Queen, the Royal Family, and the Crowned Heads and Presidents of the countries represented at the Congress had been honoured, Lord Moran, in his usual felicitous fashion, proposed the toast of the Lord Mayor and Corporation of London. No visit to London or England, he said, was complete unless one dined in the Mansion House with the Lord Mayor, to whom they were deeply grateful for the opportunity of being able to do so. In reply the Lord Mayor thanked Lord Moran for proposing the time-honoured triple toast of the Lord Mayor, the Sheriffs, and the Corporation of London. The office of Lord Mayor was comparatively recent to those of the Sheriffs, having been instituted in 1189. It was in 1753 that the building of the Mansion House was completed and they would be celebrating their bicentenary in the Coronation year. The Mansion House had four different departments. It was the official residence of the Lord and Lady Mayoress and also their private quarters. It was a law court, and, fourthly, it was a prison. It was the only building in the whole world which had such a desirable series of accommodations. The Mansion House had often been described as the home of great causes, and many ancient charities had been founded in a building which was the focal point of the British Empire. The Lady Mayoress and he wished those present a very warm welcome and especially those from overseas, "meeting in our city, in our house, and in our historic chamber to-night." The toast of "internal medicine" was then proposed by Dr. A. Gigon, professor of clinical medicine and rector of Basle University. He entertained the company with the various definitions of man. Man according to Pascal was "un roseau pensant." Man had been described as "homo faber" and "homo sapiens," and by Bergson as "homo ridens." In all countries there was a mixture of the different definitions of man. Professor Gigon finally expressed his gratitude to Lady Brain and Sir Russell Brain for the trouble they had taken in organizing the Congress and to its executive committee. In reply Sir Russell Brain said that this occasion was a fitting climax to a most successful congress and thanked the many who had helped to make it so, in particular Sir Harold Boldero, who as a centre for co-ordination far surpassed the cerebellum.

Medical Research Council.—Four new members of the Medical Research Council have been appointed, one of them a layman. The layman is Sir Geoffrey Vickers, V.C. He is a solicitor, and has been a member of the National Coal Board since 1948; previously he was legal adviser to the Coal Board. During the last war he was director-general of the economic advisory branch of the Foreign Office and Ministry of Economic Warfare. The new scientific members are Professor G. R. Cameron, F.R.S., professor of morbid anatomy at University College Hospital Medical School, London; Professor A. J. Lewis, professor of psychiatry in the University of London; and Sir James C. Spence, Nuffield professor of child health in the University of Durham.

Chartered Society of Physiotherapy.—Sir Russell Brain, P.R.C.P., was the principal guest at the annual dinner of the Chartered Society of Physiotherapy, held at the Connaught Rooms on September 19. In suggesting that physiotherapy was known, if not understood, in the Elizabethan age, Sir Russell Brain quoted from *Midsummer Night's Dream*; from *The Tempest*, where Prospero's command to Ariel, "Go, charge my goblins that they grind their joints with dry convulsions; shorten up their sinews with aged cramps," might be interpreted as a reference to osteo-arthritis; and from *Hamlet*, who exclaimed, "The time is out of joint," and, realizing that he was no orthopaedic surgeon, went on, "O cursèd spite, that ever I was born to set it right," although ultimately he found the remedy in physiotherapy, "Ay, there's the rub." In more serious vein Sir Russell Brain spoke of the satisfying character of the physiotherapist's work. Medicine, he said, was passing through a phase of rapid evolution, with enormous advances in diagnosis and treatment, and this had meant that thousands of people who were not themselves doctors had learned to carry out various procedures in the service of medicine. All these disciplines were the children of medicine, in the sense that if it were not for medicine they would not exist. There were so many of them that the National Health Service was rather in the position of the old woman who lived in a shoe. But, on the other hand, if these disciplines had not come into existence, medicine would be in many respects where it was fifty years ago. Dr. W. S. C. Copeman, in proposing the health of the Society, said that the Society had gone on from strength to strength, both numerically and in achievement. He was told by friends at the Ministry of Health that physiotherapists now constituted no fewer than one-fifth of the whole-time personnel employed in the National Health Service, and, with the exception of nursing, physiotherapy was the largest of the medical ancillary professions. A response was given by Professor J. Whillis, chairman of the Society's council, and the toast of "The Guests" was proposed by Sir Harry Platt, the president of the Society. Toasts were also drunk to the founders of the Society and to the new students.

National Health in Egypt.—Reports from Cairo state that the premier, Major-general Neguib, has asked the Royal Egyptian Medical Association to submit proposals for a national health plan. This request was put before the association's general assembly by the commandant of the Egyptian Army Medical Corps, Major-general Agrama. He told the meeting that the premier wished the association to study the British health service and to determine whether free medical care for all citizens was within the nation's means. (At present there is at least one free Government hospital in each of the provincial capitals. The country areas are served by "health centres" which generally include laboratory facilities and some maternity beds, each centre catering for a population of 10,000 to 20,000.)

The Pope on Morality in Medicine.—The Pope addressed the First International Congress of the Histopathology of the Nervous System, which was held in Rome from September 8-13, on the moral limits which should be observed in experimental and practical medicine. He discussed the extent to which the interests of science, the patient, or the community could be held to justify methods of treatment and research. In one part of his address the Pope spoke critically of certain aspects of psycho-analytical theory and practice.

Fewer Doctors in U.S. Armed Forces.—During the second world war the proportion of medical officers to troops in the American armed Forces was at the relatively high level of 5 doctors to every 1,000. At the end of the war the corresponding figure for the British armed Forces was about 3½ per 1,000. Now a Government committee in Washington announces that since the start of the Korean war the ratio in the American Forces has been reduced to 3.7 doctors to every 1,000 troops.

Dr. Andrew Topping, dean of the London School of Hygiene and Tropical Medicine, has been installed as president of the Society of Medical Officers of Health.

Dame Hilda Lloyd, president of the Royal College of Obstetricians and Gynaecologists, is one of the 87 applicants this month for the freedom by redemption of the City of London. Her application is through the Society of Apothecaries.

Major-General P. H. Mitchiner has been elected president of the Casualties Union. This is a voluntary organization of trained "casualties" who help teachers of first aid by staging accidents and acting as realistic casualties. The address of the Casualties Union is 29, Whyteleafe Hill, Whyteleafe, Surrey.

COMING EVENTS

Society of Apothecaries of London.—The Liverymen of the Worshipful Society of Apothecaries of London have been summoned to meet at Guildhall on Monday, September 29, at 10.30 a.m., to elect a Lord Mayor of the City of London for the year ensuing.

Leeds Medical School.—Professor Matthew Stewart will deliver the inaugural lecture, entitled "A Pathologist Goes Round the World," on October 16. The dinner for new students will be held on October 4.

Child Health Services Conference.—A conference on the integration of the child health services will be held at Highgate Wing of Whittington Hospital, Dartmouth Park Hill, London, N.19, on October 11 from 2.30 to 6 p.m. Professor Alan Moncrieff will be in the chair, and there will be contributions from a general practitioner, a school medical officer, a paediatrician, and a divisional treatment officer. Admission by ticket only, obtainable from the paediatric department of the hospital.

Military Medicine.—The 59th annual meeting of the Association of Military Surgeons of the United States will be held in Washington, D.C., from November 17 to 19. Following the meeting there will be a two-day international clinical symposium for visitors from abroad. This will be held in the various Government hospitals and medical centres in the Washington area.

Friends of Vellore.—The annual reunion of the Friends of Vellore will be held on October 8 at the Caxton Hall, S.W.1, at 3.30 p.m. and 6.30 p.m. Speakers will include Dr. Paul Brand, Mrs. Margaret Brand, and Dr. Gwenda Lewis. Dr. Brand will show his new coloured film "New Life Through New Hands" at the evening meeting. Full details may be obtained from Miss Marjorie Chapman, Friends of Vellore, Annandale, North End Road, London, N.W.11.

Service for Doctors.—A special service to mark the opening of the academic year will be held at All Souls' Church, Langham Place, on Sunday, October 19, at 11 a.m. Seats will be reserved for doctors who apply for tickets to the Church secretary, All Souls' Vestry, Langham Place, W.1, not later than October 16.

Wessex Rahere Club.—The autumn dinner of the Wessex Rahere Club will take place at the Grand Spa Hotel, Clifton, Bristol, on Saturday, October 25. Further details can be obtained from the hon. secretary, Mr. A. Daunt Bateman, 3, The Circus, Bath.

Contraceptive Technique.—Lectures and demonstrations on living models on contraceptive technique will be given by Marie C. Stopes, Ph.D., at the Mothers' Clinic, 108, Whitfield Street, London, W.1, at 2.30 p.m. on October 2, November 6, and December 4. Tickets, limited to medical practitioners, must be obtained in advance.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, September 29

●ROYAL COLLEGE OF SURGEONS OF ENGLAND: FACULTY OF ANAESTHETISTS, Lincoln's Inn Fields, London, W.C.—9.45 a.m. and 11.15 a.m., *"Physical Problems in Anaesthesia,"* by Dr. H. G. Enstein: 2.30 p.m., *"Functional Anatomy of the Air Passages,"* by Dr. R. Machray; 4 p.m., *"Respiration During Clinical Anaesthesia,"* by Dr. H. J. V. Morton.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—5.15 p.m., *"The Surgery of the Spleen,"* by Mr. A. H. Hunt; 6.30 p.m., *"Intestinal Obstruction in Childhood,"* by Mr. G. H. Macnab.

Tuesday, September 30

●ROYAL COLLEGE OF SURGEONS OF ENGLAND: FACULTY OF ANAESTHETISTS, Lincoln's Inn Fields, London, W.C.—9.45 a.m. and 11.15 a.m., *"The Modification of Respiration by Pathological and Clinical Factors,"* by Dr. A. I. Parry Brown; 2.30 p.m., *"Pathological Conditions Modifying Cardiovascular Physiology and Anatomy,"* by Dr. H. Rink; 4 p.m., *"Clinical Problems in Anaesthesia for Cardiac Surgery,"* by Dr. H. Rink.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—5.15 p.m., *"Endometriosis,"* by Mr. Dougias MacLeod; 6.30 p.m., *"Surgery of the Pancreas,"* by Mr. Rodney Smith.

Wednesday, October 1

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—5.30 p.m., *"Histology of Normal Skin,"* by Dr. H. Haber.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND: FACULTY OF ANAESTHETISTS, Lincoln's Inn Fields, London, W.C.—9.45 a.m. and 11.15 a.m., *"The Effects of General Anaesthesia on Cardiovascular Function,"* by Dr. J. Gillies; 2.30 p.m., *"The Clinical Implications of Hypotensive Techniques,"* by Dr. J. Gillies; 4 p.m., *"Neuromuscular and Synaptic Block,"* by Dr. T. Cecil Gray.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—5.15 p.m., *"The Uses of Cerebral Angiography,"* by Mr. J. Pennybacker; 6.30 p.m., *"Surgery of the Endocrines,"* by Mr. L. R. Broster.

SOCIETY OF PUBLIC ANALYSTS AND OTHER ANALYTICAL CHEMISTS.—At Chemical Society's rooms, Burlington House, Piccadilly, London, W., 7 p.m., *"Spectroscopic Properties of Vitamin A: Application to the Assay of Cod Liver Oil,"* by Dr. H. R. Cama and Professor R. A. Morton, F.R.S.; *"The Estimation of Carbonyl Compounds by Semicarbazide and Hydroxylamine with Special Reference to Fatty Acid Oxidation Products,"* by Mr. A. J. Feuell, B.Sc., A.R.I.C., and Mr. J. H. Skellon, M.Sc., Ph.D., F.R.I.C.; *"Simultaneous Determination of Pentose and Hexose,"* by Mr. W. R. Fernell and Mr. H. K. King, Ph.D.

YORKSHIRE SOCIETY OF ANAESTHETISTS.—At Leeds General Infirmary, 8 p.m., *"New Developments in Muscle-Relaxant Drugs,"* by Dr. H. O. J. Collier.

Thursday, October 2

●HUNTERIAN SOCIETY.—At 41, Portland Place, London, W., 6 to 8 p.m., annual party.

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—5.30 p.m., *"Mycology—Diagnosis of Mycotic Infections,"* by Dr. R. W. Riddell.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND: FACULTY OF ANAESTHETISTS, Lincoln's Inn Fields, London, W.C.—9.45 a.m., *"Neurological Mechanism in Anaesthesia,"* by Professor E. A. Pask; 11.15 a.m., discussion on Professor Pask's and Dr. Gray's lectures; 2.30 p.m., *"The Clinical Implications of Relaxant Techniques,"* by Dr. T. Cecil Gray; 4 p.m., *"General Considerations and Pharmacology of the Local Analgesics,"* by Dr. C. A. Keele.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—5.15 p.m., *"Reconstructive Surgery of Burns,"* by Mr. Richard Battle; 6.30 p.m., *"Cleft Palate,"* by Mr. Denis Browne.

Friday, October 3

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—5.30 p.m., *"Eczema,"* clinical demonstration by Dr. J. E. M. Wigley.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND: FACULTY OF ANAESTHETISTS, Lincoln's Inn Fields, London, W.C.—9.45 a.m. and 11.15 a.m., *"Some Specific Nerve Blocks, their Anatomy and Technique,"* by Dr. W. W. Mushin; 2.30 p.m. and 4 p.m., *"Spinal and Epidural Analgesia,"* by Professor R. R. Macintosh.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—5.15 p.m., *"Peripheral Arterial Grafting,"* by Mr. H. G. Eastcott.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Bolton.—On September 9, 1952, at the Bristol Maternity Hospital, to Joyce (formerly Baker), wife of Dr. F. G. Bolton, a daughter—Eleanor Mary.

Clark.—On September 7, 1952, to Mary Rose (formerly Harris), wife of Dr. David Clark, of Bromley, Kent, a son—Alan Trelawney.

Davies.—On September 17, 1952, at Ashleigh Elmfield Park, Gosforth, Northumberland, to Mary (formerly Whiteaway), wife of Dr. Leslie Davies, a brother for Michael.

Morgan.—On September 12, 1952, at Royal Infirmary, Salisbury, to Barbara (formerly Shipley), wife of Dr. H. D. S. Morgan, a son.

DEATHS

Allworthy.—On September 13, 1952, Samuel William Allworthy, M.D.I., of Holly Villa, 3, Winston Gardens, Belfast, aged 85.

Fergusson.—On August 29, 1952, at Carnlia, Salen, Acharacle, Argyll, Duncan Fergusson, M.B., Ch.B.

Parry.—On September 7, 1952, at Annfield Plain, Co. Durham, Richard Parry, L.R.C.P.&S.Ed., aged 67.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Is Chloramphenicol Safe?

Q.—*In view of the reports of fatal aplastic anaemia following the use of chloramphenicol (see Journal, July 19, p. 136) will you please advise when it is justifiable to prescribe this drug? Should an alternative be chosen whenever possible?*

A.—The mere fact that an occasional case of fatal aplastic anaemia has been recorded following the use of chloramphenicol in no way contraindicates its use in cases in which it is otherwise indicated. Sulphonamides have been known to cause aplastic anaemia, and indeed no potent drug exists without undesirable side-effects, which do not, however, invalidate their use. The bacteriologist, after testing the sensitivity of the infecting organism, will usually indicate which antibiotic should be employed. When the organism is equally sensitive to penicillin it should be employed in preference to chloramphenicol, as penicillin is cheaper and less liable to cause side-effects. The use of chloramphenicol is usually indicated in the treatment of typhoid and paratyphoid fevers, infections due to the haemophilus group of organisms (*H. influenzae* and *H. pertussis*), and in rickettsial infections. Certain virus infections can also be controlled by chloramphenicol.

Thiouracil and Agranulocytosis

Q.—*What are the risks of agranulocytosis after methyl thiouracil? I have a man of 39 on 50 mg. daily who refuses to have a blood count done.*

A.—The risk of agranulocytosis occurring in the course of treatment with thiouracil or its derivatives depends on the particular thiouracil used, the dose administered and the period during which it is administered. The highest recorded incidence for relatively large doses of thiouracil itself is about 1 in 60. With methyl thiouracil and the much smaller doses now used, the risk is much less, probably less than 1 in 200.

Although most textbooks recommend periodic leucocyte counts to recognize agranulocytosis, more and more observers are coming to regard such counts as unnecessary, because temporary depressions of the leucocyte count are very common and unimportant, while true agranulocytosis has an abrupt onset in which the leucocytes may fall to low levels within a few hours. The patient should be warned: "If you feel ill while taking these tablets, and especially if you develop a temperature or a sore throat, stop taking the tablets and come to see me (or ask me to visit you) on the same day."

Treatment of Senile Languor

Q.—*Are drugs of any value in combating mental sluggishness and forgetfulness in the aged? If so, what regime is recommended?*

A.—There is evidence that in old age the normal metabolic processes in individual cells are depressed. The nervous system usually gives evidence of this before other organs are affected, so that some degree of forgetfulness and mental sluggishness is normal in old people. The extent of the disability and the age of onset vary considerably, however, in different persons.

Old people, especially those living on an inadequate income, often take an unsatisfactory diet, and since in addition many have achlorhydria some degree of vitamin deficiency is always a possibility. At least three vitamins—aneurin, nicotinic acid, and riboflavin are concerned with carbohydrate metabolism, and there is evidence that improvement in the mental state of the aged may occur after giving supplements of the vitamin-B complex together with vitamin C. There can be no harm in giving these substances in full doses, but unless a fairly rapid response occurs it is unlikely that long-continued administration will have any effect. Nicotinic acid is not only a vitamin but also a vasodilator, and it is possible that some of the beneficial results reported after its use are the result of a better cerebral blood supply. The dose is 50 mg. by mouth, and up to 500 mg. a day may be given, but the patient should be warned that the face may flush.

Amphetamine and dextro-amphetamine have been given to the aged in an attempt to revive their flagging mental processes. These drugs may have a striking effect on physical and mental inertia. One drawback to their use is that they diminish appetite, but this may even be an advantage if the patient is obese; another is the tendency for their effect to diminish with time. Finally, the patient may come to rely on them and relapse to a state of torpor when administration ceases.

Prolonged Barbiturate Therapy

Q.—*What ill effects may follow the prolonged use of barbiturates in therapeutic dosage?*

A.—Moderate doses of short-acting barbiturates can usually be taken almost indefinitely without ill effect. Habituation may of course become established and some degree of tolerance may develop, so that larger doses may be necessary to produce sleep. Occasionally sensitivity to barbiturates occurs resulting in drug fever and erythematous rashes. In elderly patients and in those with poor renal function the long-acting barbiturates, such as phenobarbitone, may in time produce cumulative effects resulting in undue drowsiness and depression.

Loss of Desire in Women

Q.—*What are the most frequent causes of loss of a previously normal libido in the female, and how should such a case be investigated? The patient in question is 35, has been happily married for seven years, but since her husband went overseas during the war she has lost her libido. A psychiatrist has told her that she has transferred her love from her husband to their only child. This she does not believe, and she resents the suggestion.*

A.—Although cessation or diminution of ovarian activity can cause secondary sexual frigidity, it usually does not, and if it were operating in this case there would be other obvious manifestations, such as amenorrhoea and atrophy of the genitalia. Likewise, causes such as severe general ill-health and debility would be easily recognized. In nearly all cases of loss of libido the cause is psychological or environmental in character, and the explanation this woman has been given is probably near the truth although perhaps too limited and unnecessarily harsh.

Prolonged separation of the partners commonly leads to temporary frigidity and impotence. The birth of a child, and especially the first one, is nearly always followed by some loss of desire on the part of the woman for a variable period of time. Achievement of a fundamental objective of coitus, the awakening of mother love with some readjustment of the emotions, extra work, and anxiety associated with looking after the baby, etc., all play a part. Ordinarily, however, a normal libido returns when the period of physical and nervous stress passes, and as the child becomes more independent. In this case, therefore, two groups of factors may be operating. Unfortunately, it is not stated how long it is since the confinement and the return of the husband. If adequate time for readjustment has elapsed then it is quite possible that the mother's attentions are too much focused on the child or other interests. Again, there may be other problems such as housing difficulties, or the woman may for one reason or another be anxious to avoid a further

pregnancy. In the latter case, the appropriate treatment is advice on contraception. In other circumstances treatment should be by explanation and reassurance.

Oestrogen therapy is useless unless there is clear evidence of ovarian under-activity. Occasionally, small doses of androgen, say methyl testosterone. 5 mg. sublingually, each day for not longer than two months, seem to help.

Perfume Dermatitis

Q.—*What constituents of perfumes are responsible for contact dermatitis? What treatment is advised?*

A.—The manufacture of perfumes is an elaborate and complicated art. For some of the details the reader should consult *Cosmetic Dermatology*, by H. Goodman (McGraw-Hill Book Co., 1936). The ingredients are multitudinous, and to any one of them an individual may be sensitive. Among other ingredients are numerous tinctures of vegetable and animal origin, solutions of essential oils and flower pomades. It is not practical to test the patient to all ingredients. Perfumes containing eau-de-Cologne occasionally give rise to a pigmented dermatosis on exposed parts due to the effect of sunlight on oil of bergamot.

The treatment is to avoid the particular perfume to which the patient is sensitive. Sensitiveness can be demonstrated by simple patch-test to the whole perfume.

Lichen Planus of the Penis

Q.—*What is the local and general treatment for lichen planus of the glans penis in a man of 55 years?*

A.—No local treatment is necessary or desirable apart from simple cleanliness. In the unlikely event of there being much irritation a 2% carbolic lotion is advised.

It is important to be satisfied that there is no pelvic and especially prostatic disease. Lichen planus of the penis is sometimes related to marital difficulties and would seem to be of psychosomatic significance. Apart from such considerations, reassurance and general tonic measures and a good holiday with change of scene and interest are probably most helpful. There is no general treatment of specific value.

Reactions in C.S.F. after Parenteral Therapy

Q.—*Can drugs given parenterally ever be responsible for a reaction in a previously normal C.S.F.?*

A.—Drugs such as bromides or sulphonamides which pass into the cerebrospinal fluid can be detected in it after parenteral administration, but if by a "reaction" is meant an increase of cells the writer does not know of any drug which will cause this after it has been given parenterally.

Accidental Vaccinia

Q.—*A case was recently reported (Journal, May 17, p. 1067) of fatal generalized vaccinia contracted from accidental contact with an "active vaccination sore." In what way and to whom might such sores be infectious? Eczematous babies would appear to run a grave risk in mixing with newly vaccinated babies in infant welfare clinics.*

A.—Vaccinia is likely to be infectious only to those in close contact with the vaccinated individual. Thus there have been numerous instances where mothers have developed vaccinia from handling their vaccinated babies. There must presumably be some abrasion or lesion of the recipient's skin to allow the vaccinia virus to establish itself. This is the reason why eczematous children are more likely to acquire the infection by contact, and in a severe form. As in smallpox, living virus is present in the vaccinal lesion throughout its various stages, and thus the vaccinated case is potentially infective until the last crust disappears. Infection, however, is not likely to spread to other babies in a clinic unless there is intimate contact with the actual lesion. If there should be skin disease in any member of a family where a child is being vaccinated, it might be recommended that the vaccinal lesion be kept covered, although this is not the usual procedure. The most effective preventive of contact infection is, of course, to see that all children are vaccinated in infancy and again during early school life.

Vitamin K in Urticaria and Psoriasis

Q.—*How convincing is the evidence that vitamin K is useful in the treatment of urticaria and psoriasis?*

A.—The evidence is not convincing at all.

NOTES AND COMMENTS

Chronic Constipation.—Dr. A. PINEY (London, W.1) writes: The reply to the question about chronic constipation ("Any Questions?" August 30, p. 523) only briefly mentions the importance of diet "containing an adequate amount of fluid and roughage." I should like to call attention to the great value of the old remedy: an onion (preferably raw) at night and a raw apple in the morning. Few cases of chronic constipation, unless due to organic causes, fail to respond; and the unpleasant smell of the breath can be completely prevented by sucking two chlorophyll tablets after eating the onion. Equally good, although not to everybody's taste, is garlic at night, but this must be raw; it is less convenient than onion because few people will eat it without lettuce or some other salad.

OUR EXPERT writes: There is no satisfactory evidence that either raw onion, raw garlic, or raw apple are effective stimulants of the large intestine. Garlic is described in a monograph in the *B.P.C.* as having "antiseptic, diaphoretic, diuretic, and expectorant properties" and its active principle, allyl sulphide, has been administered as a bactericide and expectorant. "Allisatin," a proprietary preparation of garlic adsorbed on to activated charcoal, is said to reduce the number of Gram-positive organisms present in the stools and to relieve diarrhoea. The ordinary onion is of less strength than garlic but contains the same active principles. Cooked apples have been recommended in the treatment of constipation, but raw apples, by virtue of their high pectin content, may diminish intestinal activity. Raw pulped apple diet is still used by some physicians in severe diarrhoea and ulcerative colitis. It would therefore seem difficult to explain the beneficial effect of a raw onion and a raw apple a day in the treatment of chronic constipation. Of all the common articles of diet, the onion is probably the one which most frequently upsets the digestion in normal people. Most chronic dyspeptics learn to avoid it in any form. It is therefore somewhat surprising to hear that it is so readily accepted by patients with sluggish bowels.

Enuresis.—Dr. J. R. DAVIDSON (Bridge of Weir) writes: I was interested to note that in the reply to the question concerning enuresis ("Any Questions?" September 6, p. 574) reference was made to the paper we published in 1950. In describing the apparatus the word "bag" is a little misleading, as it is a pad consisting of a rubber sheet with wires or metal fixed to it. Since that time 70 further cases are known to us to have been treated by this method. The ages of these patients ranged from 4 to 23 years, and from the information received from various workers and parents of children the results appear to have been as follows: in 70% a good response with continued ability to keep dry; in some cases the change was dramatic after many other methods had failed, and the "cure" has been maintained. In 20% an improvement was reported, and in 10% (seven cases) this form of treatment was found of no value; among the latter were some very disturbed children who were obviously unsuitable. The most successful type of case is the intelligent child who is anxious to rid himself of a habit and who has no marked psychological difficulty or has been treated for any such difficulty.

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